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(21) International Application Number: PCT/DK00/00264 (22) International Filing Date: 16 May 2000 (16.05.00) (30) Priority Data: PA 1999 00684 17 May 1999 (17.05.99) DK PA 2000 00478 21 March 2000 (21.03.00) DK (71) Applicants: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). AGOURON PHARMACEUTICALS, INC. [US/US]; 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).	(72) Inventors: LING, Anthony; 10933 Caminito Cuesta, San Diego, CA 92131 (US). PLEWE, Michael, Bruno; Caminito Eva 4711, San Diego, CA 92130 (US). TRUESDALE, Larry, Kenneth; 10382 Rue Chamberry, San Diego, CA 92131 (US). LAU, Jesper; Rosenvænget 3, DK-3520 Farum (DK). MADSEN, Peter; Ulvebjerg 7, DK-2880 Bagsværd (DK). SAMS, Christian; Jakob Danneførds Vej 4a 1., DK-1973 Frederiksberg C (DK). BEHRENS, Carsten; Lundtoftegade 107, 1.th., DK-2200 Copenhagen N (DK). VAGNER, Josef; 12381 N. Granville Canyon Way, Oro Valley, AZ 85737 (US). CHRISTENSEN, Inge, Thøger; Kulsviertoft 52, DK-2800 Lyngby (DK). LUNDT, Behrend, Frederik; Rosenhaven 118, DK-2980 Kokkedal (DK). SIDELMANN, Ulla, Grove; Dronningengen 10A, DK-2950 Vedbæk (DK). THØGERSEN, Henning; Gregersmindevej 8, DK-3520 Farum (DK). (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: GLUCAGON ANTAGONISTS/INVERSE AGONISTS (57) Abstract A novel class of compounds, which act to antagonize the action of the glucagon hormone on the glucagon receptor. Owing to their antagonizing effect of the glucagon receptor the compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases such as hyperglycemia, Type 1 diabetes, Type 2 diabetes and obesity.		

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GLUCAGON ANTAGONISTS/INVERSE AGONISTS**FIELD OF THE INVENTION**

- 5 The present invention relates to agents that act to antagonize the action of the glucagon peptide hormone. More particularly, it relates to glucagon antagonists or inverse agonists.

BACKGROUND OF THE INVENTION

- 10 Glucagon is a key hormonal agent that, in co-operation with insulin, mediates homeostatic regulation of the amount of glucose in the blood. Glucagon primarily acts by stimulating certain cells (mostly liver cells) to release glucose when blood glucose levels fall. The action of glucagon is opposite to that of insulin, which stimulates cells to take up and store glucose whenever blood glucose levels rise. Both glucagon and insulin are peptide hormones.

- 15 Glucagon is produced in the alpha islet cells of the pancreas and insulin in the beta islet cells. Diabetes mellitus is a common disorder of glucose metabolism. The disease is characterized by hyperglycemia and may be classified as Type 1 diabetes, the insulin-dependent form, or Type 2 diabetes, which is non-insulin-dependent in character. Subjects with Type 1 diabetes are hyperglycemic and hypoinsulinemic, and the conventional treatment for this form of the disease is to provide insulin. However, in some patients with Type 1 or Type 2 diabetes, absolute or relative elevated glucagon levels have been shown to contribute to the hyperglycemic state. Both in healthy control animals as well as in animal models of Type 1 and Type 2 diabetes, removal of circulating glucagon with selective and specific antibodies has resulted in reduction of the glycemic level (Brand et al., Diabetologia 37, 985 (1994); Diabetes 43, [suppl 1], 172A (1994); Am. J. Physiol. 269, E469-E477 (1995); Diabetes 44 [suppl 1], 134A (1995); Diabetes 45, 1076 (1996)). These studies suggest that glucagon suppression or an action that antagonizes glucagon could be a useful adjunct to conventional antihyperglycemia treatment of diabetes. The action of glucagon can be suppressed by providing an antagonist or an inverse agonist, ie substances that inhibit or prevent glucagon induced responses. The antagonist can be peptidic or non-peptidic in nature. Native glucagon is a 29 amino acid peptide having the sequence:
- 20
25
30

His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-NH₂.

- 35 Glucagon exerts its action by binding to and activating its receptor, which is part of the Glucagon-Secretin branch of the 7-transmembrane G-protein coupled receptor family (Jelinek et

al., Science 259, 1614, (1993)). The receptor functions by an activation of the adenylyl cyclase second messenger system and the result is an increase in cAMP levels.

Several publications disclose peptides that are stated to act as glucagon antagonists. Probably, the most thoroughly characterized antagonist is DesHis¹[Glu⁹]-glucagon amide (Unson et al., Peptides 10, 1171 (1989); Post et al., Proc. Natl. Acad. Sci. USA 90, 1662 (1993)). Other antagonists are eg DesHis¹,Phe⁶[Glu⁹]-glucagon amide (Azizh et al., Bioorganic & Medicinal Chem. Lett. 16, 1849 (1995)) or NLeu⁹,Ala^{11,16}-glucagon amide (Unson et al., J. Biol. Chem. 269(17), 12548 (1994)).

Peptide antagonists of peptide hormones are often quite potent; however, they are generally known not to be orally available because of degradation by physiological enzymes, and poor distribution in vivo. Therefore, orally available non-peptide antagonists of the peptide hormones are preferred. Among the non-peptide glucagon antagonists, a quinoxaline derivative, (2-styryl-3-[3-(dimethylamino)propylmethylamino]-6,7-dichloroquinoxaline was found to displace glucagon from the rat liver receptor (Collins, J.L. et al., Bioorganic and Medicinal Chemistry Letters 2(9):915-918 (1992)). West, R.R. et al., WO 94/14426 (1994) discloses use of skyrin, a natural product comprising a pair of linked 9,10-anthracenedione groups, and its synthetic analogues, as glucagon antagonists. Anderson, P.L., US patent No. 4,359,474 discloses the glucagon antagonistic properties of 1-phenyl pyrazole derivatives. Barcza, S., U.S. Patent No. 4,374,130, discloses substituted disilacyclohexanes as glucagon antagonists. WO 98/04528 (Bayer Corporation) discloses substituted pyridines and biphenyls as glucagon antagonists. WO 97/16442 and US patent No 5,776,954 (Merck & Co., Inc.) disclose substituted pyridyl pyrroles as glucagon antagonists and WO 98/21957, WO 98/22108, WO 98/22109 and US 5,880,139 (Merck & Co., Inc.) disclose 2,4-diaryl-5-pyridylimidazoles as glucagon antagonists. Furthermore, WO 97/16442, US patent Nos 5,837,719 and 5,776,954 (Merck & Co., Inc.) discloses 2,5-substituted aryl pyrroles as glucagon antagonists. WO 98/24780, WO 98/24782, WO 99/24404 and WO 99/32448 (Amgen Inc.) disclose substituted pyrimidinone and pyridone compounds and substituted pyrimidine compounds, respectively, which are stated to possess glucagon antagonistic activity. Madsen et al (J. Med. Chem. 1998 (41) 5151-7) discloses a series of 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanones as competitive human glucagon receptor antagonists. WO 99/01423 (Novo Nordisk A/S) discloses a series of acylhydrazones as glucagon antagonists/inverse agonists.

These known glucagon antagonists differ structurally from the present compounds.

DEFINITIONS

The following is a detailed definition of the terms used to describe the compounds of the invention:
5

"Halogen" designates an atom selected from the group consisting of F, Cl, Br or I.

The term "C₁₋₆-alkyl" in the present context designates a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.
10

The term "C₂₋₆-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.
15

The term "C₂₋₆-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.
20
25

The term "C₁₋₆-alkoxy" as used herein, alone or in combination, refers to the radical -O-C₁₋₆-alkyl where C₁₋₆-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.
30

The term "C₁₋₆-alkanoyl" as used herein denotes a group -C(O)H or -C(O)-C₁₋₅-alkyl. Representative examples are formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl and the like.

The term "C₃₋₈-cycloalkyl" as used herein represents a carbocyclic group having from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

- 5 The term "C₃₋₈-cycloalkenyl" as used herein represents a carbocyclic group having from 3 to 8 carbon atoms containing a least one double bond. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

10

The term "C₄₋₈-cycloalkenyl" as used herein represents a carbocyclic group having from 4 to 8 carbon atoms containing a least one double bond. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

15

The term "heterocyclyl" as used herein represents a saturated or partially unsaturated 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

20

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydro-

25 genated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

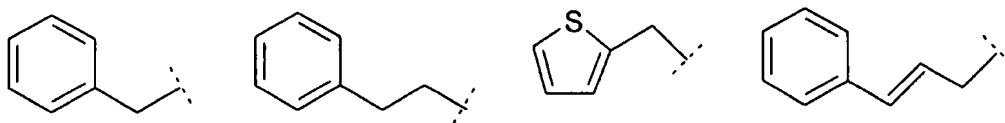
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The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-

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thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinoliziny, quinoliny, isoquinoliny, quinoxaliny, naphthyridiny, pteridiny, carbazolyl, azepiny, diazepiny, acridiny and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrroliny, pyrazoliny, indoliny, oxazolidiny, oxazoliny, oxazepiny and the like.

10 "Aryl-C₁₋₆-alkyl", "heteroaryl-C₁₋₆-alkyl", "aryl-C₂₋₆-alkenyl" etc. mean C₁₋₆-alkyl or C₂₋₆-alkenyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:



The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

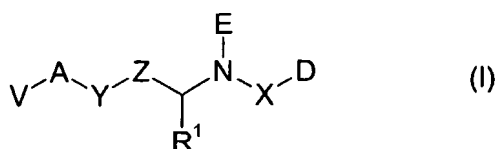
Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

Furthermore, when using the terms "independently are" and "independently selected from" it should be understood that the groups in question may be the same or different.

25 The present invention is based on the unexpected observation that the compounds of the general formula (I) disclosed below antagonize the action of glucagon.

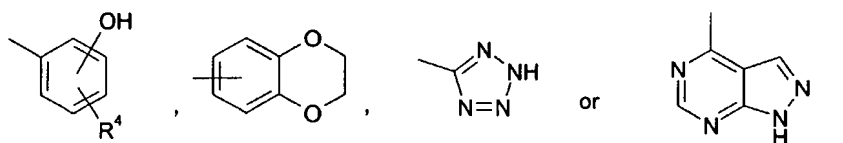
DESCRIPTION OF THE INVENTION

Accordingly, the invention is concerned with compounds of the general formula (I):



wherein

V is $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$, $-\text{S}(\text{O})_2\text{OR}^2$,



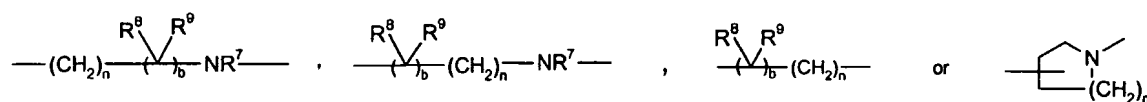
wherein

R^2 and R^3 independently are hydrogen or C_{1-6} -alkyl,

R^4 is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{OR}^5$, $-\text{NR}^5\text{R}^6$ or C_{1-6} -alkyl,

wherein R^5 and R^6 independently are hydrogen or C_{1-6} -alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

7

R^7 is hydrogen, C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl,

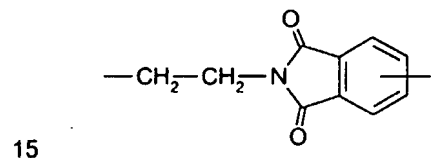
5 Y is $-C(O)-$, $-S(O)_2-$, $-O-$ or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

10 which may optionally be substituted with one or two groups R^{46} and R^{47} selected from hydrogen, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{10}$, $-NR^{10}R^{11}$ and C_{1-6} -alkyl,

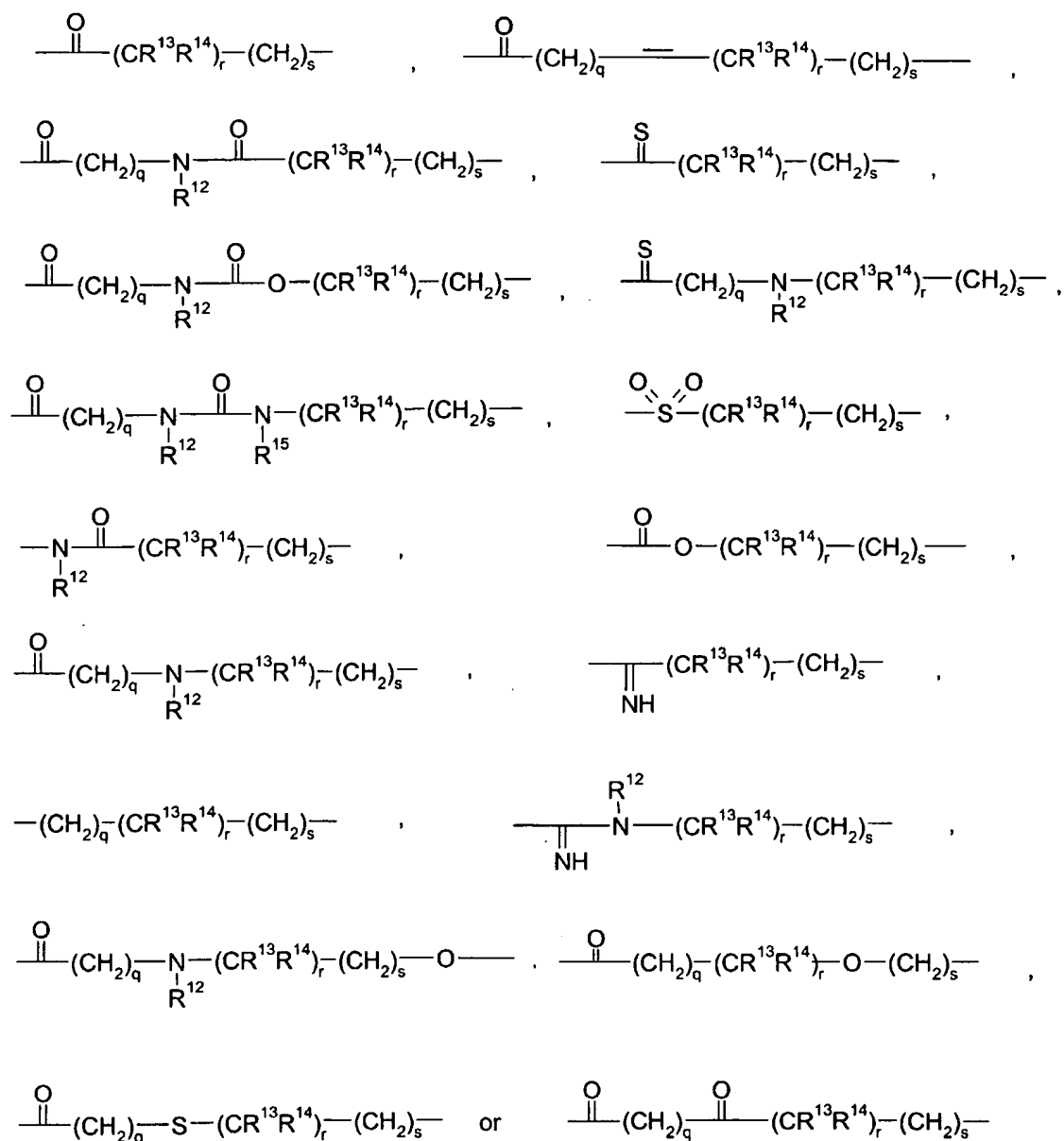
wherein R^{10} and R^{11} independently are hydrogen or C_{1-6} -alkyl,

or -A-Y-Z- together are



R^1 is hydrogen or C_{1-6} -alkyl,

X is



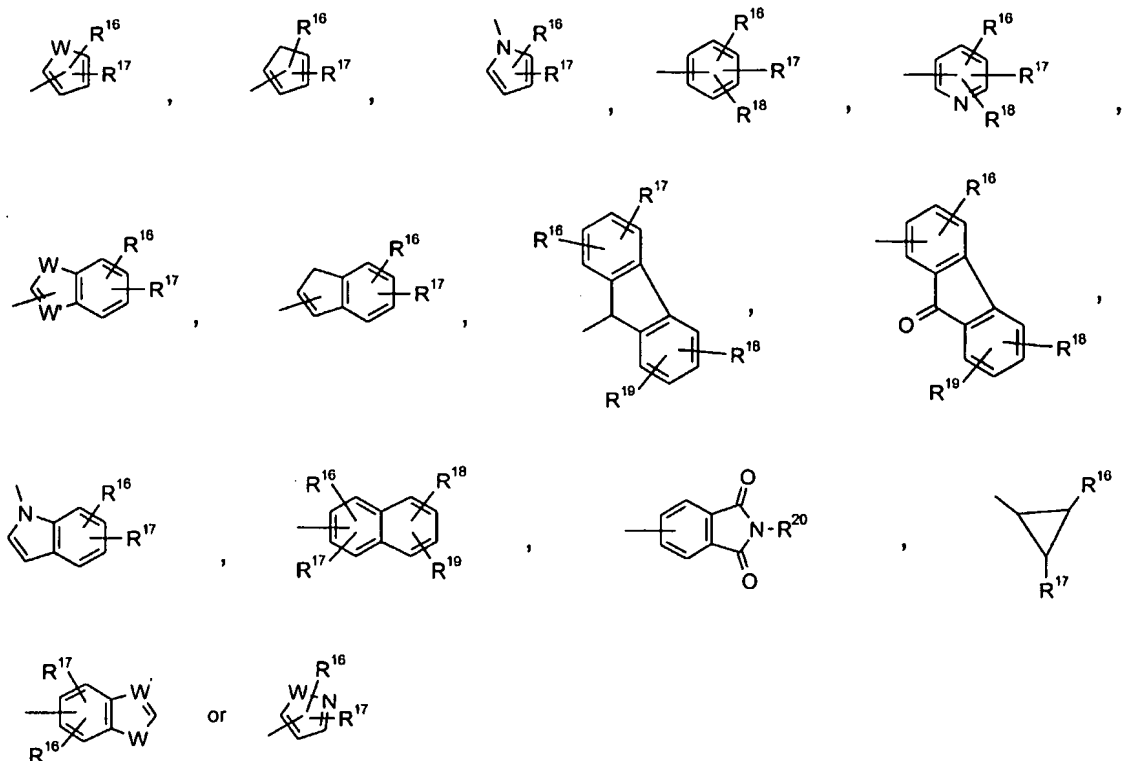
5 wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R¹², R¹³, R¹⁴ and R¹⁵ independently are hydrogen or C₁₋₈-alkyl,

D is



wherein

W is -O-, -S-, -S(O)₂- or -NR²⁰-,

W' is =CR^{20'}- or =N-,

R^{16} , R^{17} , R^{18} and R^{19} independently are

- 15 • hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹, -C(O)R²¹ or -C(O)OR²¹,

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- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -
 CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
 -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

- C₃₋₈-cycloalkyl, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyloxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio, C₃₋₈-cycloalkylthio, C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

-CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
 -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
 5 -OC(O)R²¹, -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents se-
 10 lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

15 wherein R²¹ and R²² independently are hydrogen, -CF₃, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cyclo-
 alkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl or heteroaryl,

or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom
 may form a 3 to 8 membered heterocyclic ring optionally containing one or two further het-
 20 eroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two
 double bonds,

or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge
 -(CR¹⁶R¹⁷)_a-O-(CR¹⁸R¹⁹)_c-O-,
 25

wherein

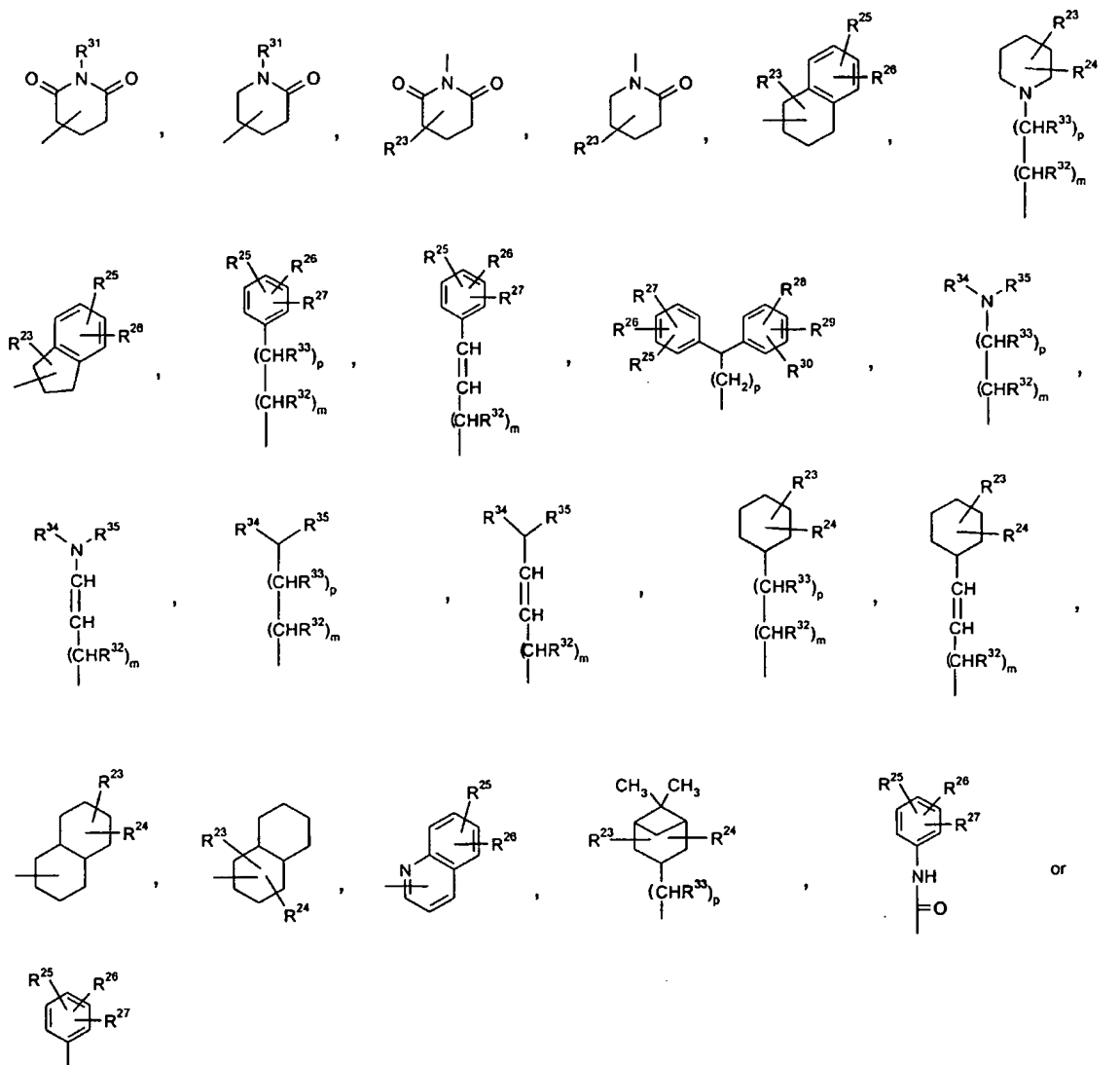
a is 0, 1 or 2,

30 c is 1 or 2,

R¹⁶, R¹⁷, R¹⁸ and R¹⁹ independently are hydrogen, C₁₋₆-alkyl or halogen,

R²⁰ and R^{20'} independently are hydrogen, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₃₋₈-cycloalkyl-C₁₋₆-
 35 alkyl,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom when present, or



wherein

10

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R²³ and R²⁴ independently are

- hydrogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 5 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ or -C(O)OR³⁶,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

10 which may optionally be substituted with one or more substituents selected from
 -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

- 15 • C₃₋₈-cycloalkyl, C₃₋₈-cycloalkylidene, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-
 C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-
 C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-
 C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

20 of which the cyclic moieties optionally may be substituted with one or more sub-
 stituents selected from

- CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 25 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

- which may optionally be substituted with one or more substituents se-
 30 lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷,
 -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and
 -C(O)OR³⁶,

- aryl, aryloxy, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -NR³⁶S(O)₂R³⁷, -S(O)₂NR³⁶R³⁷, -S(O)NR³⁶R³⁷, -S(O)R³⁶, -S(O)₂R³⁶, -OS(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂OR³⁶, -CH₂NR³⁶R³⁷, -OC(O)R³⁶, -C(O)R³⁶ and -C(O)OR³⁶,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

wherein R³⁶ and R³⁷ independently are hydrogen, C₁₋₆-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and C₁₋₆-alkyl,

wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_i-CR⁴⁰R⁴¹-(CH₂)_j-O-, -(CH₂)_i-CR⁴⁰R⁴¹-(CH₂)_j- or



wherein

5 t and l independently are 0, 1, 2, 3, 4 or 5,

R⁴⁰ and R⁴¹ independently are hydrogen or C₁₋₆-alkyl,

10 R²⁵ to R³⁰ independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl,

wherein R⁴² and R⁴³ independently are hydrogen or C₁₋₆-alkyl, or

15 R⁴² and R⁴³ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

20 R³¹, R³² and R³³ independently are hydrogen or C₁₋₆-alkyl,

R³⁴ and R³⁵ independently are

- hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkanoyl, -C(O)NR⁴⁴R⁴⁵ or -S(O)₂R⁴⁵,
- 25 • aryl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkanoyl or aryl-C₁₋₆-alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C₁₋₆-alkyl,

30 wherein R⁴⁴ and R⁴⁵ independently are hydrogen or C₁₋₆-alkyl, or

R³⁴ and R³⁵ when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

R^{34} and R^{35} when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

- 5 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

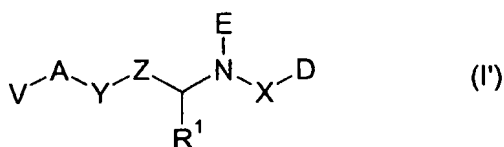
The compounds according to the invention preferably have an IC_{50} value of no greater than 5 μM as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or
 10 Glucagon Binding Assay (III) disclosed herein.

More preferably, the compounds according to the invention have a glucagon antagonistic activity as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein corresponding to an IC_{50} value of less than 1 μM ,
 15 preferably of less than 500 nM and even more preferred of less than 100 nM.

The compounds according to the invention are useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, IGT (impaired glucose tolerance), Type 2 diabetes, Type 1 diabetes and obesity.

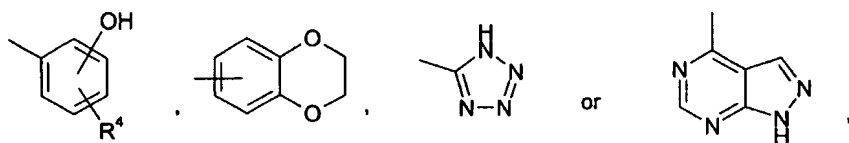
20

In a further aspect the invention relates to compounds of the general formula (I'):



25 wherein

V is $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$,



30 wherein

17

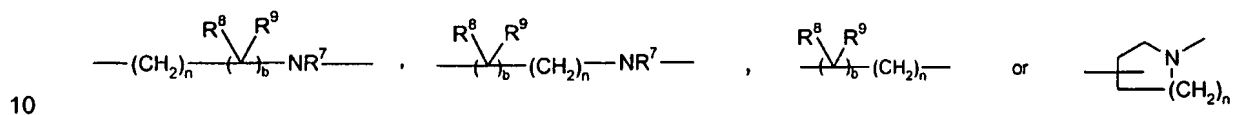
R² and R³ independently are hydrogen or C₁₋₆-alkyl,

R⁴ is hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁵, -NR⁵R⁶ or C₁₋₈-alkyl,

5

wherein R⁵ and R⁶ independently are hydrogen or C₁₋₆-alkyl;

A is



wherein

b is 0 or 1,

15

n is 0, 1, 2 or 3,

R⁷ is hydrogen, C₁₋₆-alkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl,

20 R⁸ and R⁹ independently are hydrogen or C₁₋₆-alkyl;

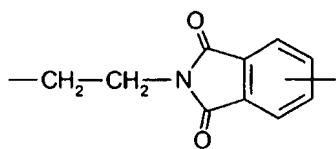
Y is -C(O)-, -S(O)₂- or -O-;

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR¹⁰, -NR¹⁰R¹¹ and C₁₋₆-alkyl,

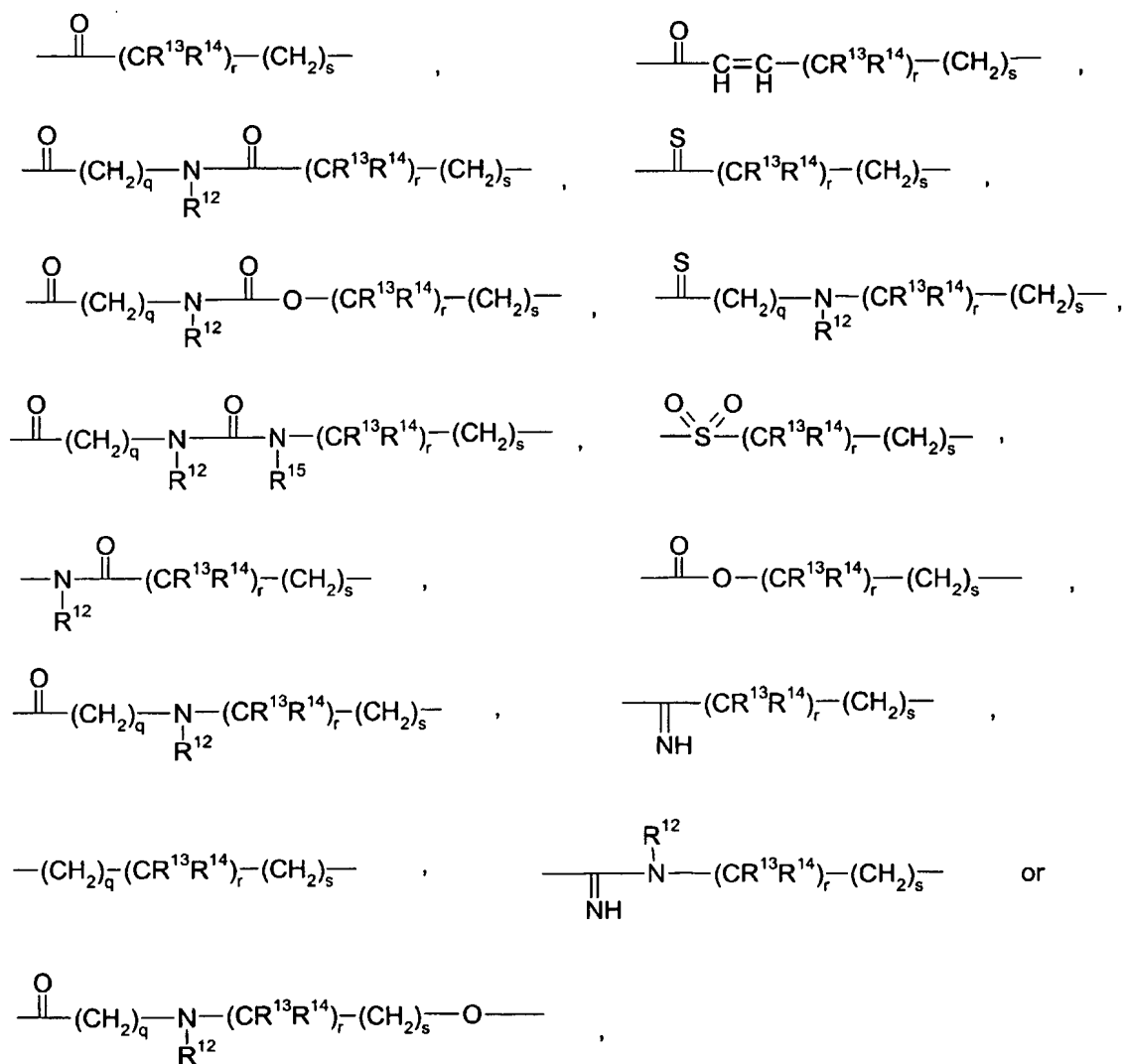
30 wherein R¹⁰ and R¹¹ independently are hydrogen or C₁₋₆-alkyl;

or -A-Y-Z- together is



R¹ is hydrogen or C₁₋₆-alkyl;

5 X is



wherein

10

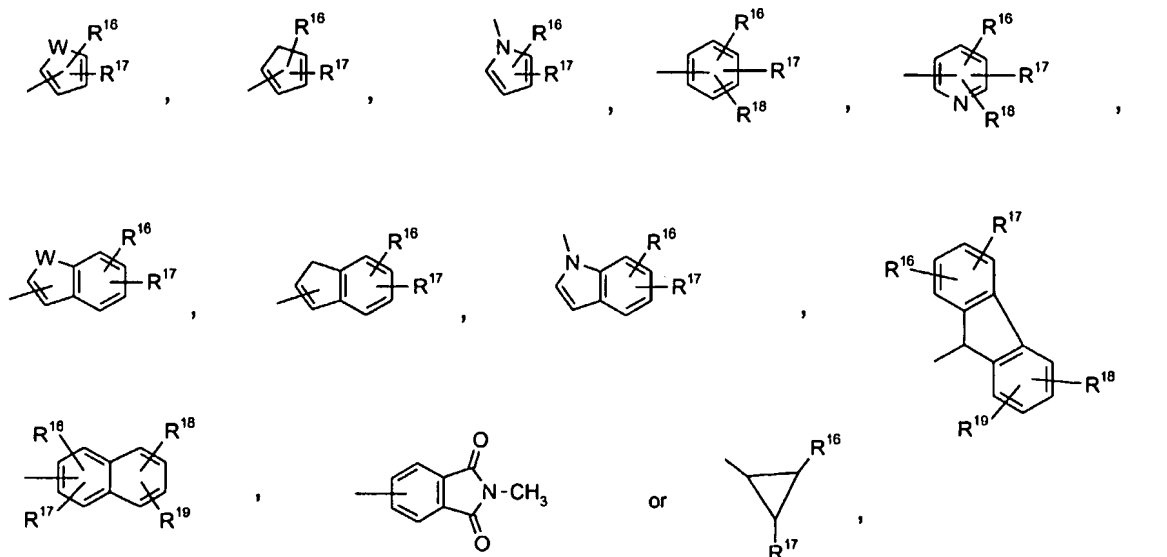
r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{12} , R^{13} , R^{14} and R^{15} independently are hydrogen or C_{1-6} -alkyl;

5

D is



10 wherein

W is -O-, -S- or -NR²⁰-,

wherein R^{20} is hydrogen or C_{1-6} -alkyl,

15

R^{16} , R^{17} , R^{18} and R^{19} independently are

hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 20 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹,
 -C(O)R²¹ or -C(O)OR²¹,

C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from -
 CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
 -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
 5 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

C₃₋₈-cycloalkyl, C₃₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl,
 C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₃₋₈-cycloalkenyl-C₁₋₆-alkyl,
 C₃₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, heterocy-
 10 clyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more sub-
 stituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 15 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents se-
 20 lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

25 aryl, aryloxy, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, het-
 eroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one
 or more substituents selected from halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃,
 30 -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²²,
 -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹,
 -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²², -CH₂C(O)NR²¹R²²,
 -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹, -C(O)R²¹ and
 -C(O)OR²¹,

35

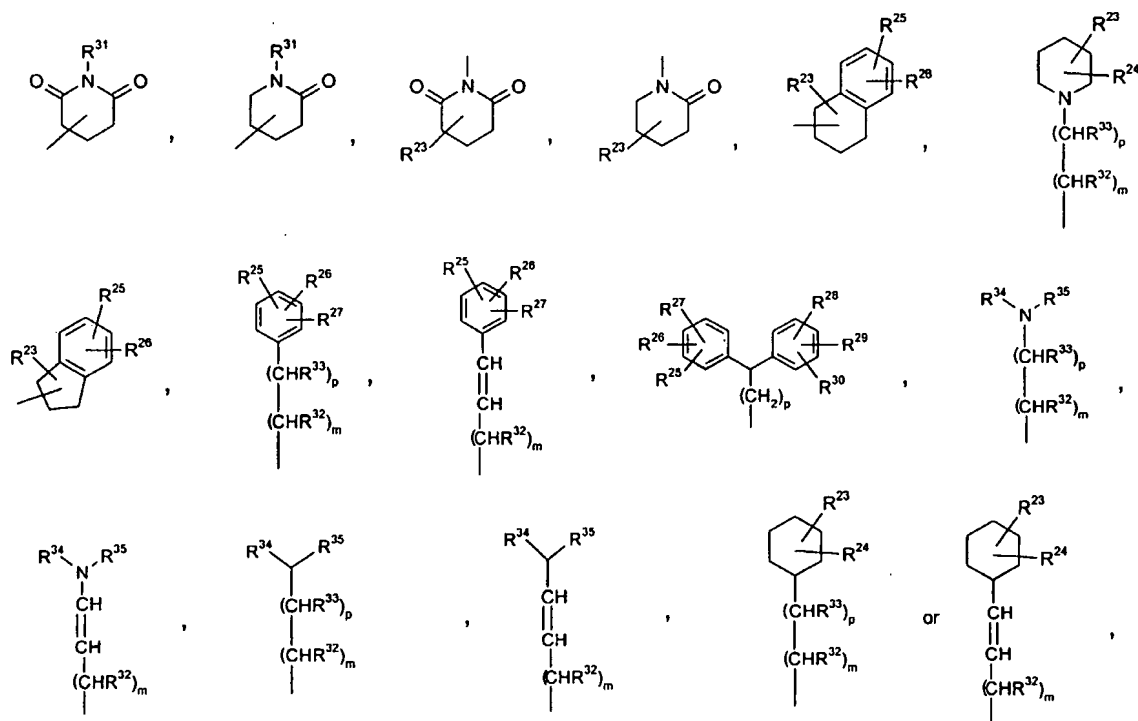
C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

5 which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

10 wherein R²¹ and R²² independently are hydrogen or C₁₋₆-alkyl, or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

15 or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge -OCH₂O- or -OCH₂CH₂O-;

20 E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R²³ and R²⁴ may be attached to the same or different ring carbon atoms and wherein a group R³¹ may be attached to a ring nitrogen atom when present, or



wherein

5 m and p independently are 0, 1, 2, 3 or 4,

R^{23} and R^{24} independently are hydrogen, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ or $-\text{C(O)}\text{OR}^{36}$,

10

C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from -
 CHF_2 , $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$,
 15 $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$,
 $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

15

C_{3-8} -cycloalkyl, C_{3-8} -cycloalkenyl, heterocyclyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

C_{3-8} -cycloalkyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkyl- C_{2-6} -alkynyl, C_{3-8} -cycloalkenyl- C_{1-6} -alkyl,

20

C_{3-8} -cycloalkenyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkynyl, heterocyclyl- C_{1-6} -alkyl, heterocyclyl- C_{2-6} -alkenyl or heterocyclyl- C_{2-6} -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$,
 5 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$,
 10 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

15 aryl, aryloxy, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkyl, aryl- C_{2-6} -alkenyl, aryl- C_{2-6} -alkynyl, heteroaryl, heteroaryl- C_{1-6} -alkyl, heteroaryl- C_{2-6} -alkenyl or heteroaryl- C_{2-6} -alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from halogen, $-\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$,
 20 $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{OS(O)}_2\text{CF}_3$, $-\text{SCF}_3$, $-\text{NO}_2$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{NR}^{36}\text{S(O)}_2\text{R}^{37}$, $-\text{S(O)}_2\text{NR}^{36}\text{R}^{37}$, $-\text{S(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{OS(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{CH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{CH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{CH}_2\text{OR}^{36}$, $-\text{CH}_2\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{R}^{36}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

25 C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$,
 30 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

wherein R^{36} and R^{37} independently are hydrogen, C_{1-6} -alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and C₁₋₆-alkyl,

5 wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two
10 double bonds,

or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l-O-, -(CH₂)_l-CR⁴⁰R⁴¹-(CH₂)_t- or
-S-(CH₂)_l-CR⁴⁰R⁴¹-(CH₂)_t-S-,
15

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

20 R⁴⁰ and R⁴¹ independently are hydrogen or C₁₋₆-alkyl,

R²⁵ to R³⁰ independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C₁₋₆-alkyl or C₃₋₆-cycloalkyl,

25 wherein R⁴² and R⁴³ independently are hydrogen or C₁₋₆-alkyl,

R³¹, R³² and R³³ independently are hydrogen or C₁₋₆-alkyl,

R³⁴ and R³⁵ independently are hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkanoyl, -C(O)NR⁴⁴R⁴⁵
30 or -S(O)₂R⁴⁵,

aryl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkanoyl or aryl-C₁₋₆-alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C₁₋₆-alkyl,
35

wherein R⁴⁴ and R⁴⁵ independently are hydrogen or C₁₋₆-alkyl,

or R³⁴ and R³⁵ when attached to the carbon atom together with the said carbon atom may
5 form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected
from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

or R³⁴ and R³⁵ when attached to the nitrogen atom together with the said nitrogen atom may
10 form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroa-
toms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double
bonds;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of
these or a pharmaceutically acceptable salt thereof;

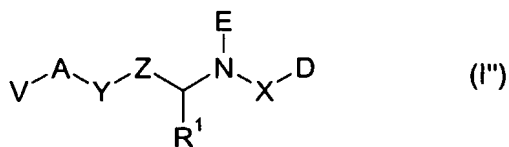
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having an IC₅₀ value of no greater than 5 μM as determined by the Glucagon Binding Assay
(I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein.

By a compound of the general formula (I') having an IC₅₀ value of no greater than 5 μM as de-
20 termined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding
Assay (III) is meant any compound of the defined formula having such activity, without limitation
to any utility or usefulness for treating any specific indication.

In a further aspect the invention relates to compounds of the general formula (I''):

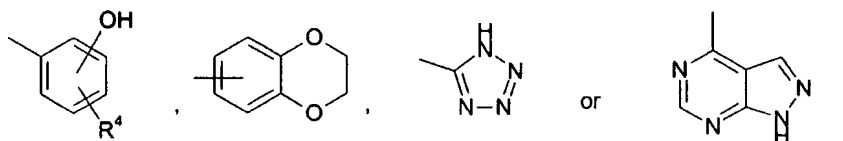
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wherein

26

V is $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$, $-\text{S}(\text{O})_2\text{OR}^2$,



wherein

5

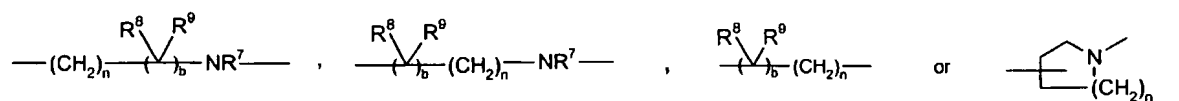
R^2 and R^3 independently are hydrogen or C_{1-6} -alkyl,

R^4 is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{OR}^5$, $-\text{NR}^5\text{R}^6$ or C_{1-6} -alkyl,

10

wherein R^5 and R^6 independently are hydrogen or C_{1-6} -alkyl,

A is



15

wherein

b is 0 or 1,

20

n is 0, 1, 2 or 3,

R^7 is hydrogen, C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl,

25

Y is $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{O}-$ or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

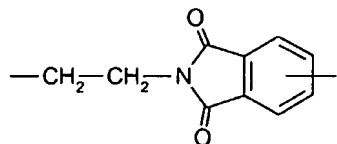
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which may optionally be attached to one or two groups R^{46} and R^{47} selected from hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{OR}^{10}$, $-\text{NR}^{10}\text{R}^{11}$ and C_{1-6} -alkyl,

27

wherein R^{10} and R^{11} independently are hydrogen or C_{1-6} -alkyl,

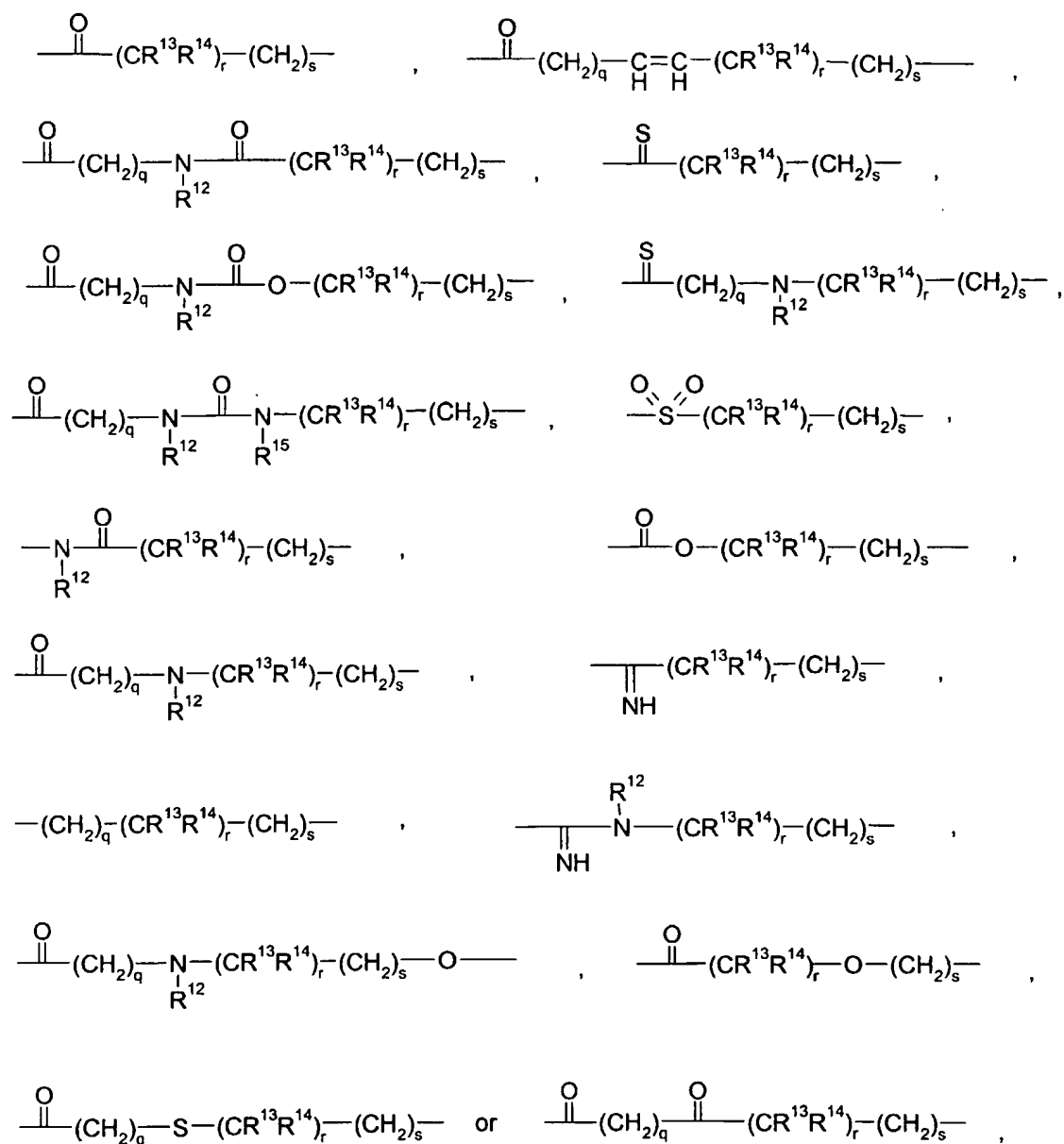
or -A-Y-Z- together are



5

R^1 is hydrogen or C_{1-6} -alkyl,

X is



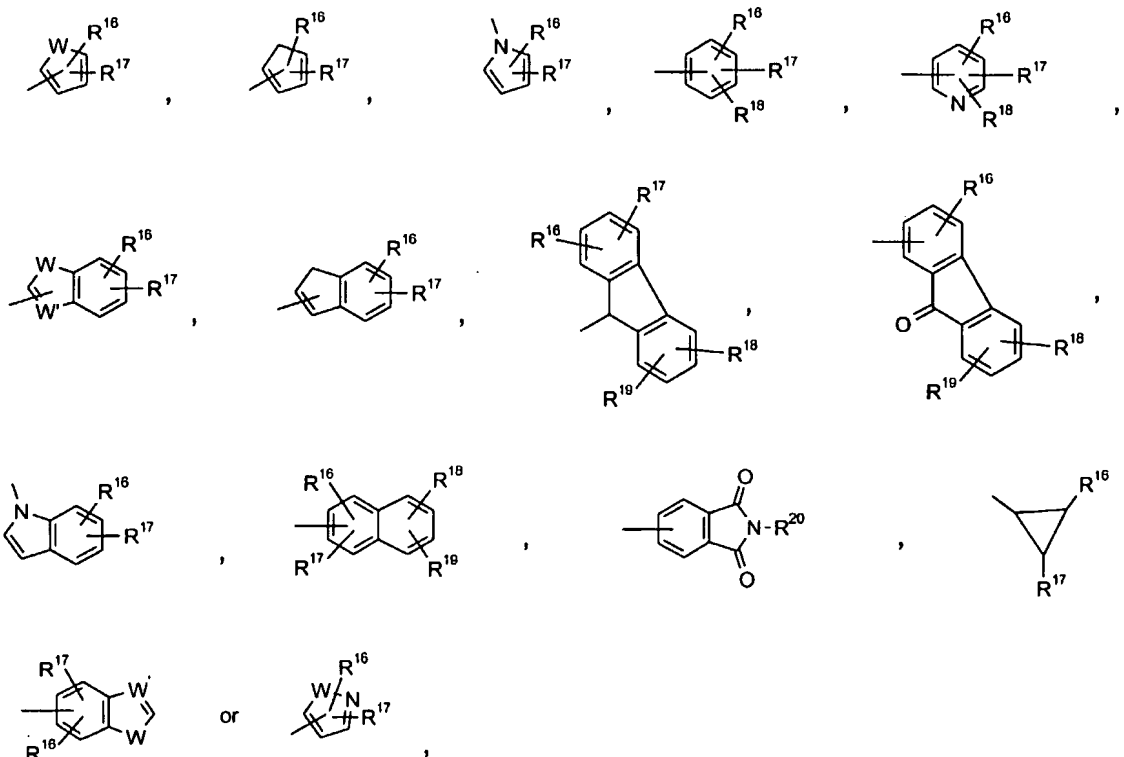
5 wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R¹², R¹³, R¹⁴ and R¹⁵ independently are hydrogen or C₁₋₈-alkyl,

D is



wherein

W is -O-, -S-, -S(O)₂- or -NR²⁰-,

10

W' is $=CR^{20'}$ - or $=N-$,

R²⁰ and R^{20'} are hydrogen, C₁₋₆-alkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl,

15 R^{16} , R^{17} , R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,

$-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$, $-\text{CH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{CH}_2\text{OR}^{21}$, $-\text{CH}_2\text{NR}^{21}\text{R}^{22}$,
 $-\text{OC}(\text{O})\text{R}^{21}$, $-\text{C}(\text{O})\text{R}^{21}$ or $-\text{C}(\text{O})\text{OR}^{21}$,

- C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

5

which may optionally be substituted with one or more substituents selected from
 $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{22}$,
 $-\text{SR}^{21}$, $-\text{S}(\text{O})\text{R}^{21}$, $-\text{S}(\text{O})_2\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{OC}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$,
 $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{C}(\text{O})\text{R}^{21}$ and $-\text{C}(\text{O})\text{OR}^{21}$,

10

- C_{3-8} -cycloalkyl, C_{3-8} -cycloalkenyl, heterocyclyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyloxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio, C_{3-8} -cycloalkylthio, C_{3-8} -cycloalkyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkyl- C_{2-6} -alkynyl, C_{3-8} -cycloalkenyl- C_{1-6} -alkyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkynyl, heterocyclyl- C_{1-6} -alkyl, heterocyclyl- C_{2-6} -alkenyl or heterocyclyl- C_{2-6} -alkynyl,

15

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

20

$-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{22}$,
 $-\text{SR}^{21}$, $-\text{S}(\text{O})\text{R}^{21}$, $-\text{S}(\text{O})_2\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{OC}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$,
 $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{C}(\text{O})\text{R}^{21}$ and $-\text{C}(\text{O})\text{OR}^{21}$,

C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

25

which may optionally be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{22}$, $-\text{SR}^{21}$, $-\text{S}(\text{O})\text{R}^{21}$, $-\text{S}(\text{O})_2\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{OC}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{C}(\text{O})\text{R}^{21}$ and $-\text{C}(\text{O})\text{OR}^{21}$,

30

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkyl, aryl- C_{2-6} -alkenyl, aryl- C_{2-6} -alkynyl, heteroaryl, heteroaryl- C_{1-6} -alkyl, heteroaryl- C_{2-6} -alkenyl or heteroaryl- C_{2-6} -alkynyl,

35

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 5 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
 -OC(O)R²¹, -C(O)R²¹ and -C(O)OR²¹,

10 C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 15 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

wherein R²¹ and R²² independently are hydrogen, -CF₃, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl or heteroaryl, or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8
 20 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge
 25 -(CR¹⁶R¹⁷)_a-O-(CR¹⁸R¹⁹)_c-O-,

wherein

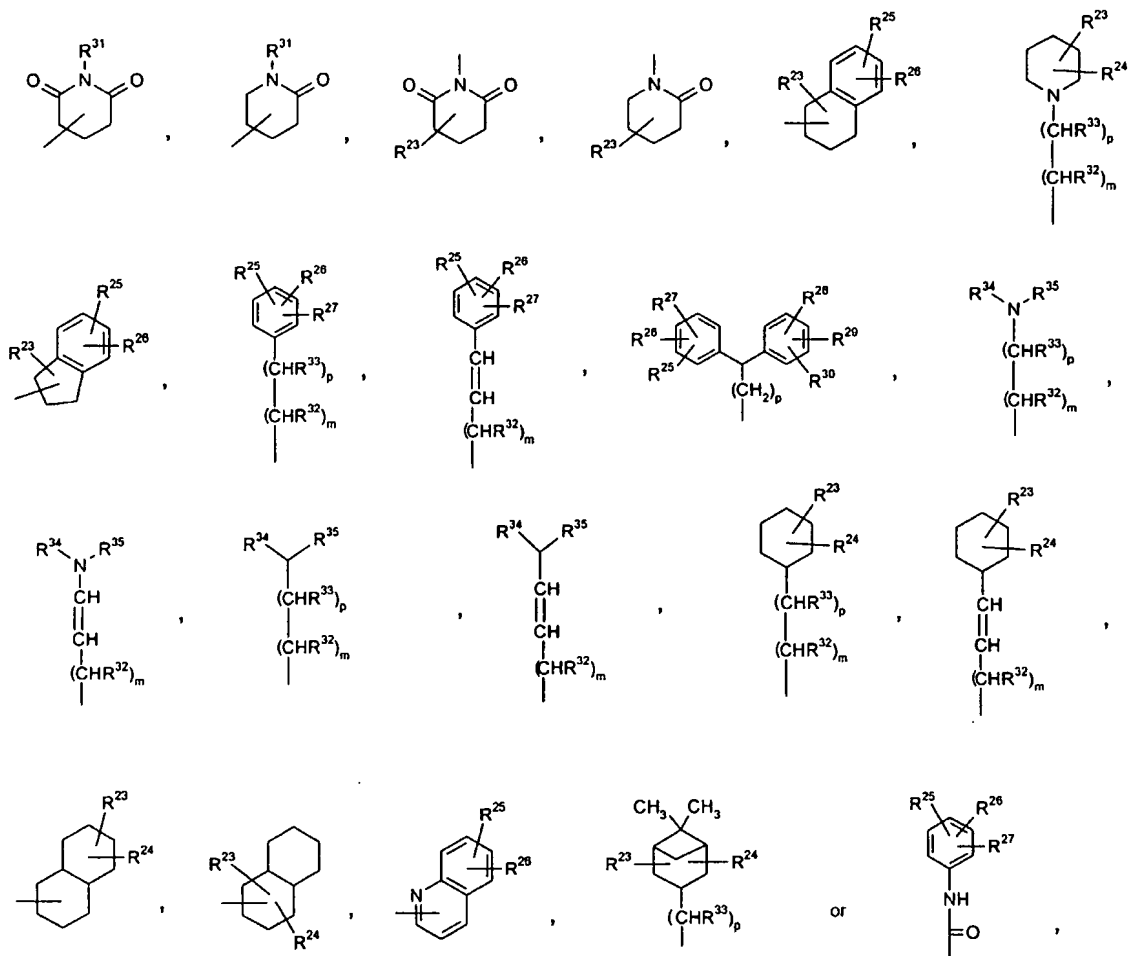
a is 0, 1 or 2,

c is 1 or 2,

R¹⁶, R¹⁷, R¹⁸ and R¹⁹ independently are hydrogen, C₁₋₆-alkyl or halogen,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom

5 when present, or



wherein

10 m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R^{23} and R^{24} independently are

- hydrogen, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ or $-\text{C(O)}\text{OR}^{36}$,

- 5 • C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from

- 10 $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

- 15 • C_{3-8} -cycloalkyl, C_{3-8} -cycloalkylidene, C_{3-8} -cycloalkenyl, heterocyclyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, C_{3-8} -cycloalkyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkyl- C_{2-6} -alkynyl, C_{3-8} -cycloalkenyl- C_{1-6} -alkyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkynyl, heterocyclyl- C_{1-6} -alkyl, heterocyclyl- C_{2-6} -alkenyl or heterocyclyl- C_{2-6} -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

- 20 $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

25

which may optionally be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

30

- aryl, aryloxy, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkyl, aryl- C_{2-6} -alkenyl, aryl- C_{2-6} -alkynyl, heteroaryl, heteroaryl- C_{1-6} -alkyl, heteroaryl- C_{2-6} -alkenyl or heteroaryl- C_{2-6} -alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

5 halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -NR³⁶S(O)₂R³⁷, -S(O)₂NR³⁶R³⁷,
 -S(O)NR³⁶R³⁷, -S(O)R³⁶, -S(O)₂R³⁶, -OS(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷,
 -NR³⁶C(O)R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂OR³⁶, -CH₂NR³⁶R³⁷,
 -OC(O)R³⁶, -C(O)R³⁶ and -C(O)OR³⁶,

10 C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷,
 15 -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and
 -C(O)OR³⁶,

wherein R³⁶ and R³⁷ independently are hydrogen, C₁₋₆-alkyl or aryl,

20 of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and
 C₁₋₆-alkyl,

wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

25 or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

30 or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_l-CR⁴⁰R⁴¹-(CH₂)_l-O-, -(CH₂)_l-CR⁴⁰R⁴¹-(CH₂)_l- or
 -S-(CH₂)_l-CR⁴⁰R⁴¹-(CH₂)_l-S-,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

5 R^{40} and R^{41} independently are hydrogen or C_{1-6} -alkyl,

R^{25} to R^{30} independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{3-8} -cycloalkenyl,

10 wherein R^{42} and R^{43} independently are hydrogen or C_{1-6} -alkyl, or

R^{42} and R^{43} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two
15 double bonds,

R^{31} , R^{32} and R^{33} independently are hydrogen or C_{1-6} -alkyl,

R^{34} and R^{35} independently are

20

- hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkanoyl, -C(O)NR⁴⁴R⁴⁵ or -S(O)₂R⁴⁵,
- aryl, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkanoyl or aryl- C_{1-6} -alkyl,

25 of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C_{1-6} -alkyl,

wherein R^{44} and R^{45} independently are hydrogen or C_{1-6} -alkyl, or

30 R^{34} and R^{35} when attached to the carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

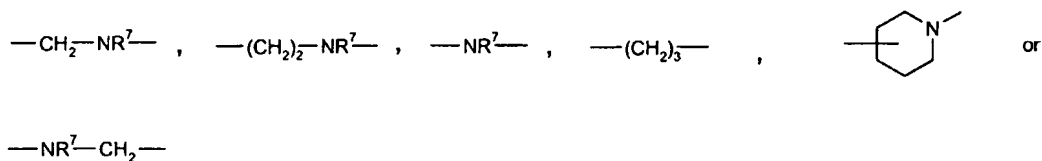
R^{34} and R^{35} when attached to the nitrogen atom together with the said nitrogen atom may
35 form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroa-

toms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment V is $-\text{C}(\text{O})\text{OH}$, $-\text{S}(\text{O})_2\text{OH}$, $-\text{C}(\text{O})\text{NHOH}$ or 5-tetrazolyl, and more preferred $-\text{C}(\text{O})\text{OH}$ or 5-tetrazolyl.

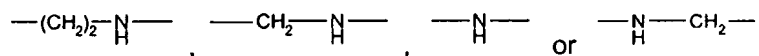
10 In a preferred embodiment A is



wherein R^7 is as defined for formula (I).

15

More preferred A is

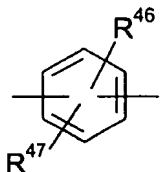


20 In a preferred embodiment Y is $-\text{C}(\text{O})-$.

In another preferred embodiment Y is a valence bond.

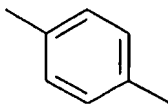
In a preferred embodiment Z is

25



wherein R^{46} and R^{47} are as defined for formula (I).

More preferably, Z is

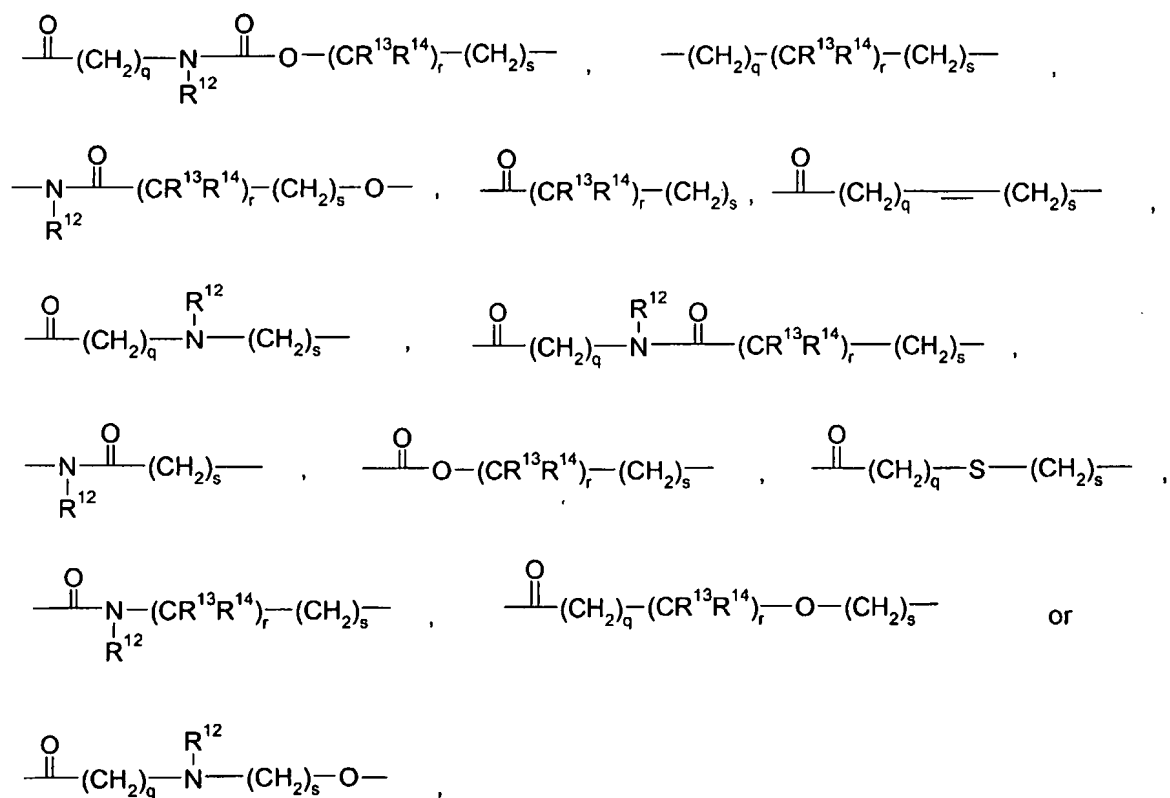


- 5 In a preferred embodiment R^1 is hydrogen.

In another preferred embodiment R^1 is methyl.

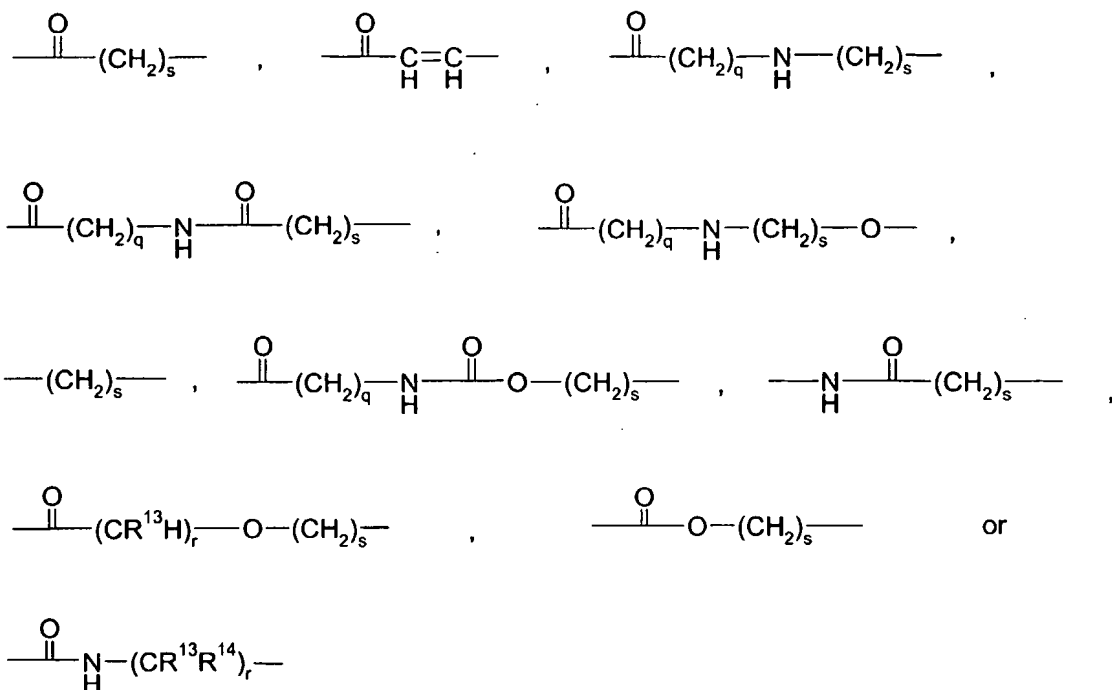
In a preferred embodiment X is

10



wherein q, r, s, R^{12} , R^{13} and R^{14} are as defined for formula (I).

More preferably, X is



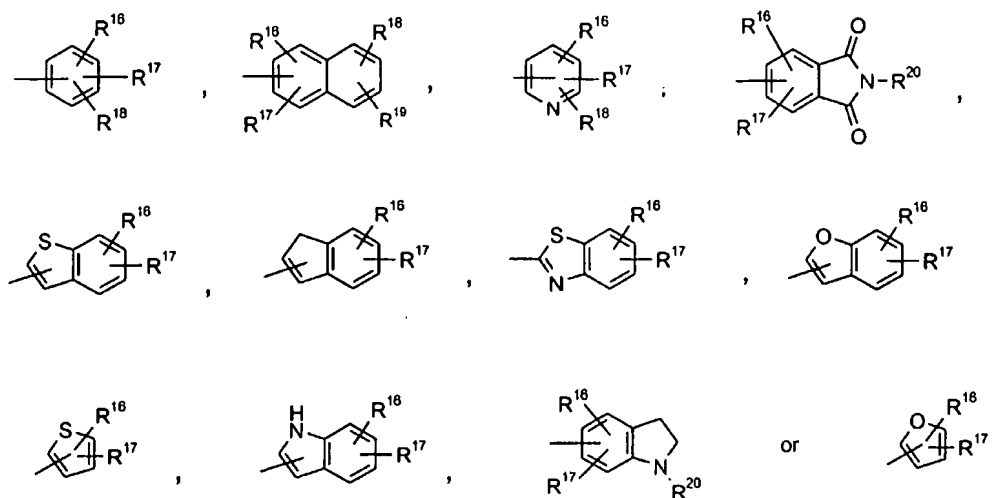
- 5 wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R¹³ is hydrogen or C₁₋₆-alkyl.

Even more preferably, X is -C(O)NH-, -C(O)NHCH₂-, -C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -C(O)CH=CH-, -(CH₂)_s-, -C(O)-, -C(O)O- or -NHC(O)-, wherein s is 0 or 1.

- 10 Still more preferably, X is -C(O)NH-, -C(O)NHCH₂-, -C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -(CH₂)_s-, -C(O)- or -NHC(O)-.

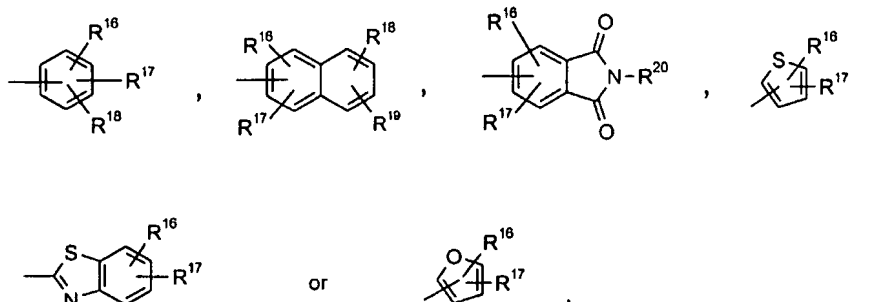
Of these X is preferably -C(O)NH- or -C(O)NHCH(CH₃)-.

In a preferred embodiment D is



- 5 wherein R^{16} , R^{17} , R^{18} , R^{19} and R^{20} are as defined for formula (I).

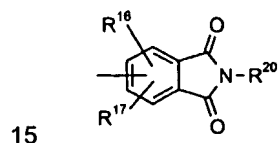
More preferably, D is



10

- wherein R^{16} , R^{17} , R^{18} and R^{20} are as defined for formula (I).

In a preferred embodiment D is



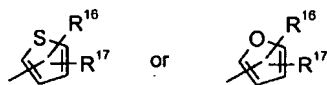
15

- wherein R^{16} , R^{17} and R^{20} are as defined for formula (I).

More preferably, R^{16} and R^{17} are both hydrogen and R^{20} is C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl. Even more preferably, R^{20} is cyclopropylmethyl, butyl or isopropyl, especially preferred isopropyl.

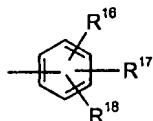
5

In another preferred embodiment D is



10 wherein R^{16} and R^{17} are as defined for formula (I).

In yet another preferred embodiment D is



15

wherein R^{16} , R^{17} and R^{18} are as defined for formula (I).

Preferably, R^{16} , R^{17} and R^{18} are independently

20 hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, hydroxy, -SCF₃, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkyl substituted with -S(O)₂R²¹, C_{1-6} -alkoxy, -S- C_{1-6} -alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio or C_{3-8} -cycloalkylthio,

25 wherein R^{21} and R^{22} independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, phenyl, phenyl- C_{1-6} -alkyl, 2,3-dihydroindolyl or isoindolyl, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidine ring,

30 phenoxy, phenoxycarbonyl, phenyl, phenyl- C_{1-6} -alkoxy, phenyl- C_{1-6} -alkyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -CN, -CF₃, -OCF₃, -NO₂, -C(O)OR²¹, -OR²¹, -NR²¹R²² or C_{1-6} -alkyl, wherein R^{21} and R^{22} independently are hydrogen or C_{1-6} -alkyl, or

wherein R^{16} and R^{17} in adjacent positions form the radical $-O-CH_2-O-$, $-CF_2-O-CF_2-O-$ or $-O-CF_2-CF_2-O-$, and R^{18} is hydrogen.

5 More preferably, R^{16} , R^{17} and R^{18} are independently

hydrogen, halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkyl substituted with $-S(O)_2R^{21}$, C_{1-6} -alkoxy, $-S-C_{1-6}$ -alkyl, $-C(O)OR^{21}$, $-C(O)R^{21}$, $-CH_2(O)R^{21}$, $-C(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-S(O)_2CF_3$, $-S(O)_2NR^{21}R^{22}$, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio or C_{3-8} -cycloalkylthio,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, phenyl or 2,3-dihydroindolyl, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidine ring,

15

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, $-C(O)OR^{21}$ or C_{1-6} -alkyl, wherein R^{21} is hydrogen or C_{1-6} -alkyl, or

20 wherein R^{16} and R^{17} in adjacent positions form the radical $-CF_2-O-CF_2-O-$ or $-O-CF_2-CF_2-O-$, and R^{18} is hydrogen.

Even more preferably, R^{16} , R^{17} and R^{18} independently are

25 hydrogen, halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkoxy, $-S-C_{1-6}$ -alkyl, $-C(O)OR^{21}$, $-C(O)R^{21}$, $-CH_2(O)R^{21}$, $-C(O)NR^{21}R^{22}$, $-S(O)_2R^{21}$, $-(O)_2CF_3$ or $-S(O)_2NR^{21}R^{22}$,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, phenyl or 2,3-dihydroindolyl,

30

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, $-C(O)OR^{21}$ or C_{1-6} -alkyl, wherein R^{21} is hydrogen or C_{1-6} -alkyl, or

35

wherein R^{16} and R^{17} in adjacent positions form the radical $-CF_2-O-CF_2-O-$ or $-O-CF_2-CF_2-O-$, and R^{18} is hydrogen.

Still more preferably, R^{16} , R^{17} and R^{18} are independently hydrogen, halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6} -alkyl, C_{1-6} -alkoxy, $-S-C_{1-6}$ -alkyl, $-C(O)OC_{1-6}$ -alkyl, $-S(O)_2C_{1-6}$ -alkyl, $-S(O)_2CF_3$, $-C(O)N(C_{1-6}\text{-alkyl})(C_{1-6}\text{-alkyl})$, $-S(O)_2N(\text{phenyl})(C_{1-6}\text{-alkyl})$, $-C(=O)C_{1-6}$ -alkyl, $-CH_2OH$, $-CH_2O(\text{tri-}C_{1-6}\text{-alkylsilyl})$, 2,3-dihydroindol-1-ylsulfonyl, phenoxy, phenyl, 4-chlorophenyl, 1,3,5-trimethylbenzyl, benzoxazolyl, 2-methyltetrazol-5-yl, 2-methyl-3-methoxycarbonylfuran-5-yl or 3-isopropyl-[1,2,4]oxadiazol-5-yl).

10

In a preferred embodiment one of R^{16} to R^{18} is hydrogen.

In another preferred embodiment two of R^{16} to R^{18} are hydrogen.

15 In yet another preferred embodiment R^{16} and R^{17} are both hydrogen and R^{18} is $-OCF_3$, $-SCF_3$, $-CF_3$, $-S(O)_2CH_3$, phenyl, halogen, C_{1-6} -alkyl, nitro, $-S-C_{1-6}$ -alkyl or $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.

20 In still another preferred embodiment R^{16} and R^{17} are both hydrogen and R^{18} is $-OCF_3$ or halogen.

In a further embodiment R^{16} is hydrogen and R^{17} and R^{18} are both halogen or are both $-CF_3$.

25 In yet a further embodiment R^{16} is hydrogen, R^{17} is $-CF_3$ and R^{18} is halogen, $-CN$, C_{1-6} -alkoxy or $-OCF_3$.

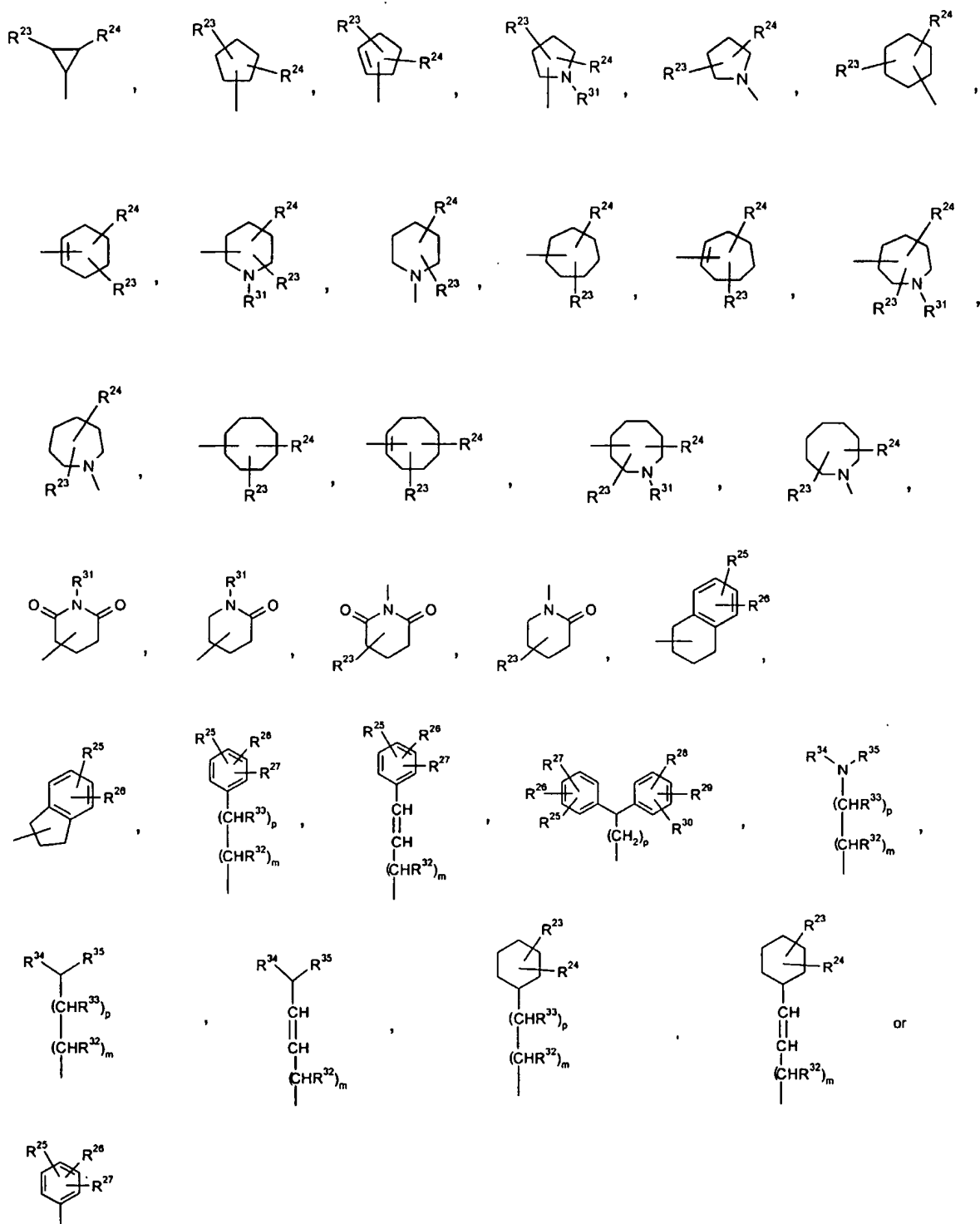
In still a further embodiment R^{16} is hydrogen, R^{17} is $-OCF_3$ and R^{18} is $-S(O)_2CH_3$, $-CH_2O\text{-tri-}C_{1-6}\text{-alkylsilyl}$, benzoxazolyl or $-CH_2OH$.

30 In another embodiment R^{16} is hydrogen, R^{17} is C_{1-6} -alkyl and R^{18} is $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.

In still another embodiment R^{16} , R^{17} and R^{18} are selected from hydrogen, $-OCF_3$, $-CF_3$, $-Br$, $-F$ and $-Cl$.

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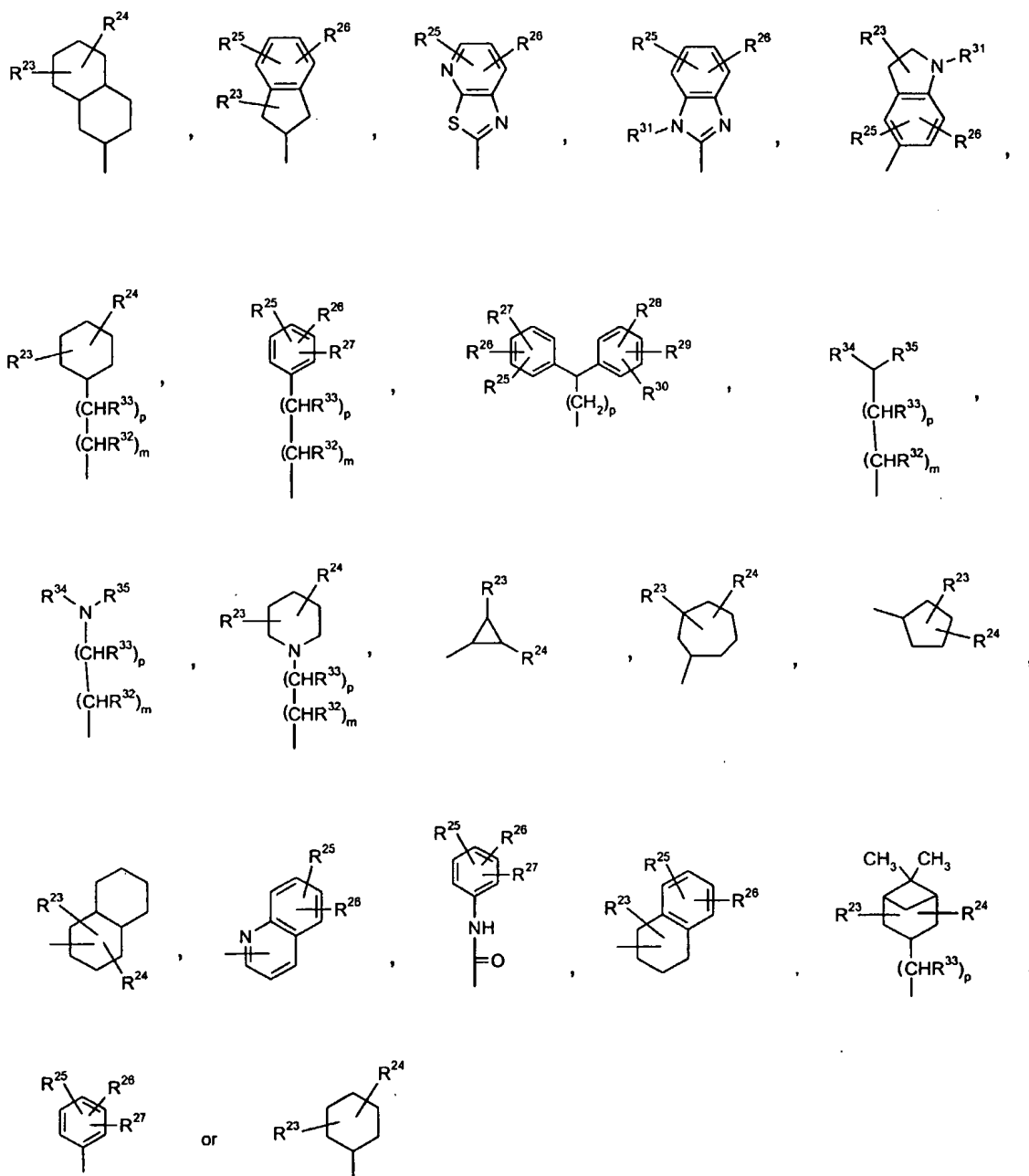
In a preferred embodiment E is



wherein

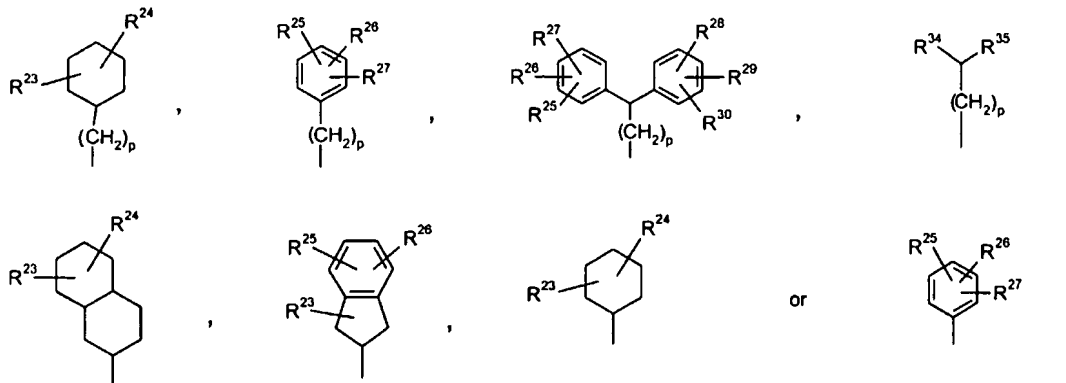
m, p and R^{23} to R^{35} are as defined for formula (I).

5 Preferably, E is



wherein m, p and R^{23} to R^{35} are as defined for formula (I).

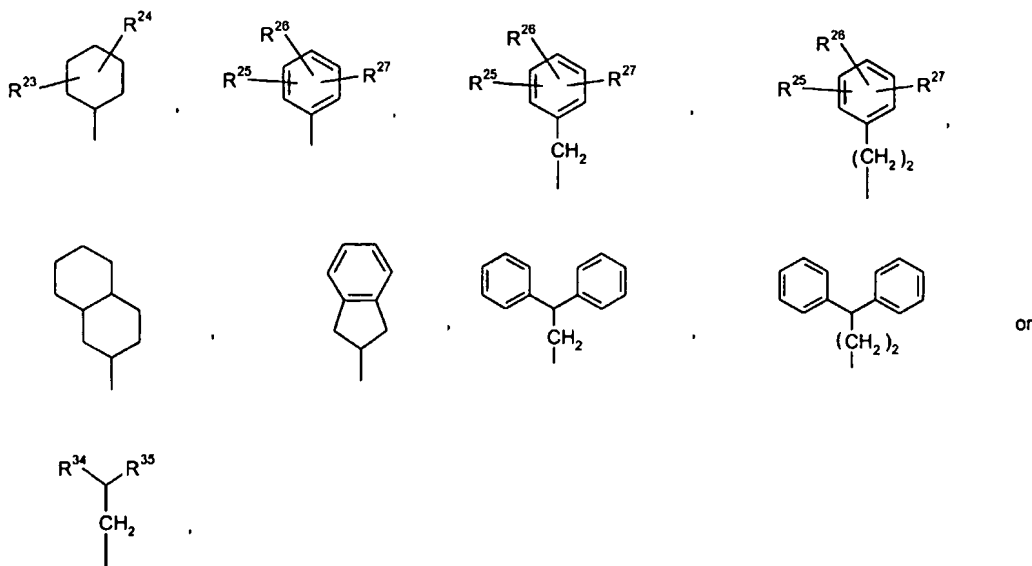
More preferably, E is



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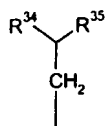
wherein p , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{34} and R^{35} are as defined for formula (I).

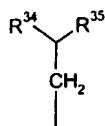
Even more preferably, E is



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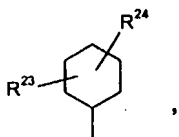
wherein R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{34} and R^{35} are as defined for formula (I).



When E is , R^{34} and R^{35} are preferably independently C_{1-6} -alkyl, hydrogen or C_{1-6} -alkoxy. More preferably, R^{34} and R^{35} are both C_{1-6} -alkyl.

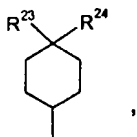
In another preferred embodiment E is

5



wherein R^{23} and R^{24} are as defined for formula (I).

10 Preferably, E is



wherein R^{23} and R^{24} are as defined for formula (I).

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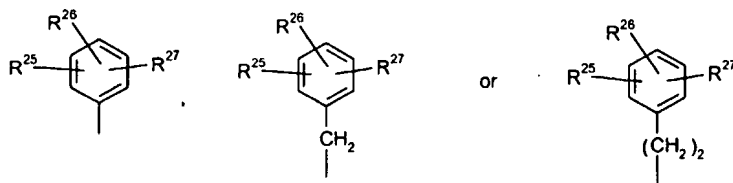
Preferably, R^{23} and R^{24} are independently selected from hydrogen, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkylidene, phenoxy, phenyl, $-C(O)NR^{36}R^{37}$ and $-OC(O)NH$ -phenyl, of which the phenyl moiety optionally may be substituted with $-OCF_3$, wherein R^{36} and R^{37} are as defined in claim 1, or R^{23} and R^{24} together form the radical $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-$, $-O-(CH_2)_l-CR^{40}R^{41}-$

20 $(CH_2)_t-O-$, $-S-(CH_2)_l-CR^{40}R^{41}-(CH_2)_l-S-$, wherein t , l , R^{40} and R^{41} are as defined for formula (I).

More preferably, R^{23} is hydrogen and R^{24} is C_{1-6} -alkyl such as *tert*-butyl or C_{3-8} -cycloalkyl such as cyclohexyl, wherein R^{23} and R^{24} are both C_{1-6} -alkyl or wherein R^{23} and R^{24} together form the radical $-(CH_2)_5-$.

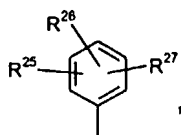
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In yet another preferred embodiment E is



5 wherein R^{25} , R^{26} and R^{27} are as defined for formula (I).

Preferably, E is



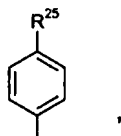
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wherein R^{25} , R^{26} and R^{27} are as defined for formula (I).

Preferably, R^{25} , R^{26} and R^{27} are independently selected from hydrogen, halogen, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-8} -cycloalkyl, C_{4-8} -cycloalkenyl, $-CF_3$, $-OCF_3$ or $-NR^{42}R^{43}$, wherein R^{42} and R^{43} are as defined for formula (I).

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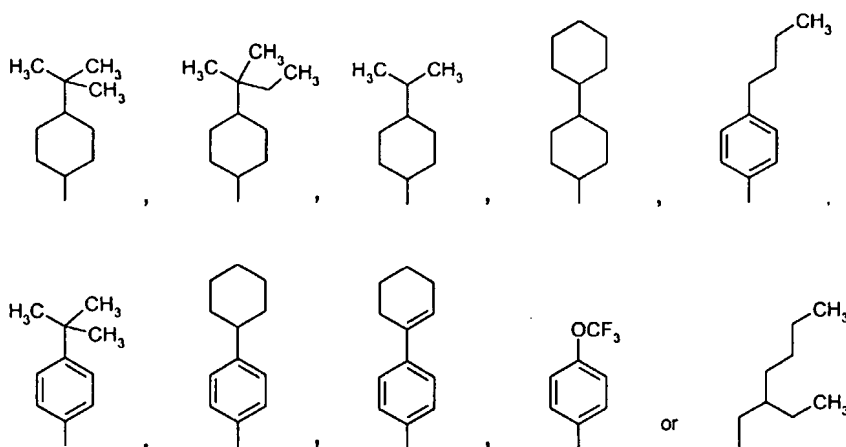
More preferably, E is



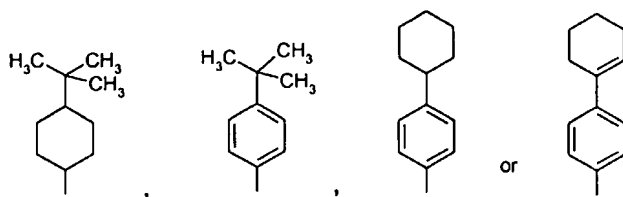
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wherein R^{25} is $-OCF_3$, $-CF_3$, C_{1-6} -alkyl such as *tert*-butyl, piperidyl, C_{3-8} -cycloalkyl such as cyclohexyl or C_{4-8} -cycloalkenyl such as cyclohexenyl.

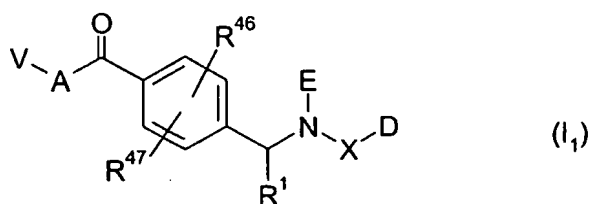
In another preferred embodiment E is



5 Of these E is preferably

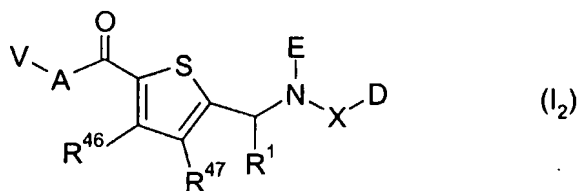


10 In one preferred embodiment the present invention relates to compounds of the general formula (I₁):



15 wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

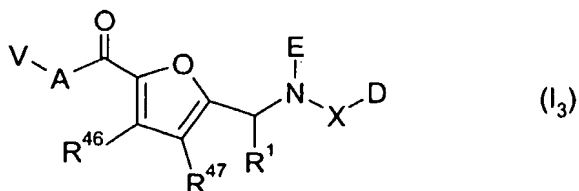
In another preferred embodiment the present invention relates to compounds of the general formula (I₂):



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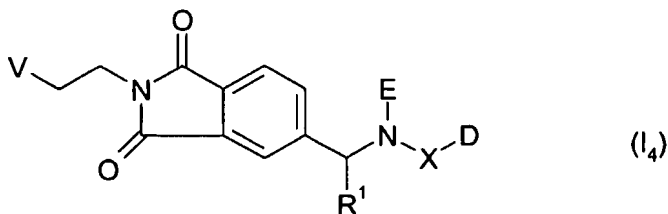
wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

10 In still another preferred embodiment the present invention relates to compounds of the general formula (I₃):



15 wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

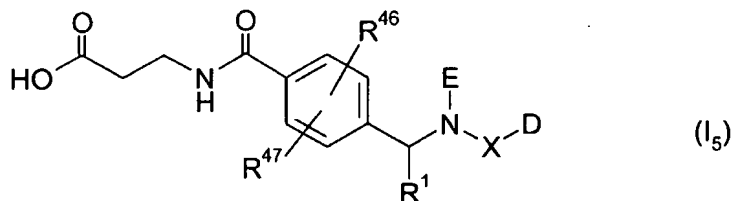
In yet another preferred embodiment the present invention relates to compounds of the general formula (I₄):



20

wherein V is -C(O)OR², -C(O)NR²R³ or -C(O)NR²OR³, and R¹, R², R³, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

In a further preferred embodiment the present invention relates to compounds of the general formula (I₅):

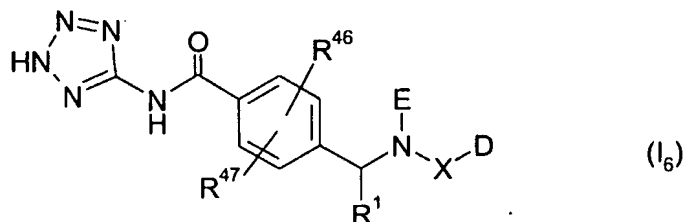


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wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

In still a further preferred embodiment the present invention relates to compounds of the general formula (I₆):

10

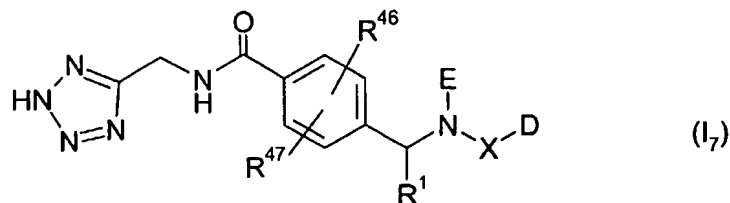


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wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

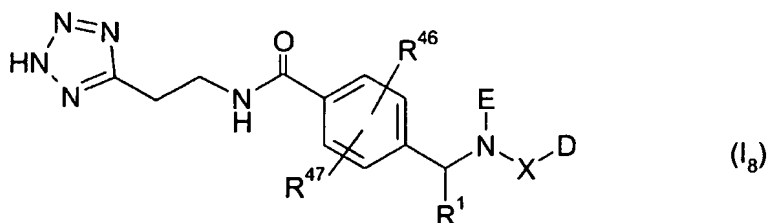
In yet a further preferred embodiment the present invention relates to compounds of the general formula (I₇):

20



wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

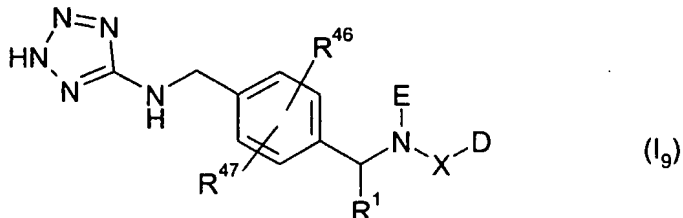
In another preferred embodiment the present invention relates to compounds of the general formula (I₈):



5

wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

- 10 In still another preferred embodiment the present invention relates to compounds of the general formula (I₉):



- 15 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

In the above formulae (I₁) to (I₃) and (I₅) to (I₉), R⁴⁶ and R⁴⁷ are preferably both hydrogen.

- 20 The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the invention.

- 25 Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may

form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms which the compounds are able to form are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pantoic, bismethylene salicylic, ethanedithionine, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Furthermore, the pharmaceutically acceptable salts comprise basic amino acid salts such as lysine, arginine and ornithine.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

5

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

10

The invention also encompasses active metabolites of the present compounds.

15

The compounds according to the present invention act to antagonize the action of glucagon and are accordingly useful for the treatment and/or prevention of disorders and diseases in which such an antagonism is beneficial.

Accordingly, in a further aspect the invention relates to a compound according to the invention for use as a medicament.

20

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients.

25

The pharmaceutical composition is preferably in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to the invention.

30

Furthermore, the invention relates to the use of a compound according to the invention for the preparation of a pharmaceutical composition for the treatment and/or prevention of a disorder or disease, wherein a glucagon antagonistic action is beneficial.

The invention also relates to a method for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention.

5

Owing to their antagonizing effect of the glucagon receptor the present compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases.

Accordingly, the present compounds may be applicable for the treatment and/or prevention of
10 hyperglycemia, IGT, insulin resistance syndromes, syndrome X, Type 1 diabetes, Type 2 diabetes, hyperlipidemia, dyslipidemia, hypertriglyceridemia, glucagonomas, acute pancreatitis, cardiovascular diseases, hypertension, cardiac hypertrophy, gastrointestinal disorders, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, etc. Furthermore, they may be applicable as diagnostic agents for identifying patients having a defect in the glucagon receptor, as
15 a therapy to increase gastric acid secretions and to reverse intestinal hypomotility due to glucagon administration.

In a preferred embodiment of the invention the present compounds are used for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

20

In yet a preferred embodiment of the invention the present compounds are used for the manufacture of a medicament for lowering blood glucose in a mammal.

In another preferred embodiment of the invention the present compounds are used for the
25 preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

In still another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

30

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

- 5 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 1 diabetes. Such treatment and/or prevention is normally accompanied by insulin therapy.

- 10 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of obesity.

In still a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of an appetite regulation or energy expenditure disorder.

15

In a further aspect of the invention the present compounds may be administered in combination with one or more pharmacologically active substances eg selected from antidiabetics, antiobesity agents, antihypertensive agents and agents for the treatment and/or prevention of complications resulting from or associated with diabetes.

20

Suitable antidiabetics comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference, as well as orally active hypoglycaemic agents.

- 25 The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, insulin sensitizers, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic
30 enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

35

In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg metformin.

In yet another embodiment the present compounds are administered in combination with a meglitinide eg repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 to Dr. Reddy's Research Foundation.

Furthermore, the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 to Dr. Reddy's Research Foundation.

In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor eg miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells eg tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a sulphonylurea and

metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the compounds according to the invention may be administered in combination
5 with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, uro-
10 cortin agonists, $\beta 3$ agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing
15 compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA (dopamine) agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.
20

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

25 In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.
30

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril,
35 quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine,

isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

- 5 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more pharmacologically active substances are considered to be within the scope of the present invention.

10 PHARMACEUTICAL COMPOSITIONS

- The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

- The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

- Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

- Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet that may be prepared by conventional tableting techniques may contain:

Core:

	Active compound (as free compound or salt thereof)	5.0 mg
	Lactosum Ph. Eur.	67.8 mg
	Cellulose, microcryst. (Avicel)	31.4 mg
5	Amberlite	1.0 mg
	Magnesii stearas Ph. Eur.	q.s.

Coating:

	HPMC approx.	9 mg
10	Mywacett 9-40 T* approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

15 If desired, the pharmaceutical composition of the invention may comprise the compound of the formula (I) in combination with further pharmacologically active substances such as those described in the foregoing.

EXPERIMENTAL

20 In the following section binding assays as well as functional assays useful for evaluating the efficiency of the compounds of the invention are described.

Binding of compounds to the glucagon receptor was determined in a competition binding assay using the cloned human glucagon receptor.

25 Antagonism was determined as the ability of the compounds to inhibit the amount of cAMP formed in the presence of 5 nM glucagon.

30 For further characterization, antagonism was determined in a functional assay, measured as the ability of the compounds to right-shift the glucagon dose-response curve. Using at least 3 different antagonist concentrations, the K_i was calculated from a Schild plot.

Glucagon Binding Assay (I)

35 Receptor binding was assayed using cloned human receptor (Lok et al., Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SS1 restriction sites

(Lok et al.) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The K_d was shown to be 0.1 nM.

- 5 Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (10 mM tris/HCl, pH 7.4 containing 30 mM NaCl, 1 mM dithiothreitol, 5 mg/L leupeptin (Sigma), 5 mg/L pepstatin (Sigma), 100 mg/L bacitracin (Sigma) and 15 mg/L recombinant aprotinin (Novo Nordisk A/S)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation upon a
10 layer of 41 w/v % sucrose at 95.000 x g for 75 min. The white band located between the two layers was diluted in buffer and centrifuged at 40.000 x g for 45 min. The precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until use.

- Glucagon was iodinated according to the chloramine T method (Hunter and Greenwood, Nature
15 194, 495 (1962)) and purified using anion exchange chromatography (Jørgensen et al., Hormone and Metab. Res. 4, 223-224 (1972)). The specific activity was 460 $\mu\text{Ci}/\mu\text{g}$ on the day of iodination. Tracer was stored at -18°C in aliquots and were used immediately after thawing.

- Binding assays were carried out in triplicate in filter microtiter plates (MADV N65, Millipore). The
20 buffer used in this assay was 50 mM HEPES, 5 mM EGTA, 5 mM MgCl_2 , 0.005% tween 20, pH 7.4. Glucagon was dissolved in 0.05 M HCl, added an equal amount (w/w) of HSA and freeze-dried. On the day of use, it was dissolved in water and diluted in buffer to the desired concentrations.

- 25 Test compounds were dissolved and diluted in DMSO. 140 μL buffer, 25 μL glucagon or buffer, and 10 μL DMSO or test compound were added to each well. Tracer (50.000 cpm) was diluted in buffer and 25 μL were added to each well. 1-4 μg freshly thawed plasma membrane protein diluted in buffer was then added in aliquots of 25 μL to each well. Plates were incubated at 30°C for 2 hours. Non-specific binding was determined with 10^{-6} M of glucagon. Bound tracer and un-
30 bound tracer were then separated by vacuum filtration (Millipore vacuum manifold). The plates were washed with 2 x 100 μL buffer/ well. The plates were air dried for a couple of hours, whereupon the filters were separated from the plates using a Millipore Puncher. The filters were counted in a gamma counter.

Functional Assay (I)

The functional assay was carried out in 96 well microtiter plates (tissue culture plates, Nunc). The resulting buffer concentrations in the assay were 50 mM tris/HCl, 1 mM EGTA, 1.5 mM MgSO₄, 1.7 mM ATP, 20 μM GTP, 2 mM IBMX (isobutyl-methyl-xanthine), 0.02% tween-20 and 0.1% HSA. pH was 7.4. Glucagon and proposed antagonist were added in aliquots of 35 μL diluted in 50 mM tris/HCl, 1 mM EGTA, 1.85 mM MgSO₄, 0.0222 % tween-20 and 0.111 % HSA, pH 7.4. 20 μL of 50 mM tris/HCl, 1 mM EGTA, 1.5 mM MgSO₄, 11.8 mM ATP, 0.14 mM GTP, 14 mM IBMX and 0.1% HSA, pH 7.4 was added. GTP was dissolved immediately before the assay.

50 μL containing 5 μg of plasma membrane protein was added in a tris/HCl, EGTA, MgSO₄, HSA buffer (the actual concentrations were dependent upon the concentration of protein in the stored plasma membranes).

The total assay volume was 140 μL. The assay was incubated for 2 hours at 37°C with continuous shaking. Reaction was terminated by addition of 25 μL 0.5 N HCl. cAMP was measured by the use of a scintillation proximity kit (Amersham).

Glucagon Binding Assay (II)

Receptor binding was assayed using the cloned human receptor (Lok et al., Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SS1 restriction sites (Lok et al.) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The K_d was shown to be 0.1 nM.

Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (50 mM tris base, pH 7.4 containing 0.32 mM sucrose, 2 mM EGTA, 1 μg/mL leupeptin, 5 μg/mL pepstatin A, 5 μg/mL aprotinin, 1 mM phenylmethylsulfonylfluoride (all from Sigma)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation. The homogenate was resuspended and centrifuged again. The final precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until use.

Binding assays were carried out in duplicate in polypropylene tubes or microtiter plates. The buffer used in this assay was 50 mM HEPES pH 7.4 containing 5 mM EGTA, 5 mM MgCl₂ and

0.005% Tween 20. Sample (glucagon (Bachem CA) or test compounds) was added to each tube or well. Tracer (~ 25.000 cpm) was diluted in buffer and was added to each tube or well. 0.5 mg freshly thawed plasma membrane protein diluted in buffer was then added in aliquots to each tube or well. Tubes or plates were incubated at 37°C for 1 hour. Non-specific binding was
5 determined with 10^{-7} M of glucagon. Bound tracer and unbound tracer were then separated by vacuum filtration. The tubes or wells were washed twice with 0.01% Triton X-100 buffer. Scintillation fluid was added to the plates and radioactivity was quantified using a scintillation counter.

Functional Assay (II)

10 The functional assay determined the ability of the compounds to antagonize glucagon-stimulated formation of cAMP in a whole-cell assay. The assay was carried out in borosilicate glass 12 x 75 tubes. The buffer concentrations in the assay were 10 mM HEPES, 1 mM EGTA, 1.4 mM $MgCl_2$, 0.1 mM IBMX, 30 mM NaCl, 4.7 mM KCl, 2.5 mM NaH_2PO_4 , 3mM glucose and 0.2% BSA. The pH was 7.4. Loose whole cells (0.5 mL, 10^6 /mL) were pretreated with various
15 concentrations of compounds for 10 min at 37°C , then challenged with glucagon for 20 min. Some aliquots (500 μ L) of cells were treated with test compounds (55 μ L) alone to test for agonist activity. The reactions were terminated by centrifugation, followed by cell lysis with the addition of 500 μ L 0.1% HCl. Cellular debris was pelleted and the supernatant containing cAMP evaporated to dryness. cAMP was measured by the use of an RIA kit (NEN, NEK-033). Some
20 assays were carried out utilizing the adenylate cyclase FlashPlate system from NEN.

Glucagon Binding Assay (III)

BHK (baby hamster kidney cell line) cells were transfected with the human glucagon receptor and a membrane preparation of the cells was prepared. Wheat Germ Agglutinin derivatized
25 SPA beads containing a scintillant (WGA beads) (Amersham) bound the membranes. ^{125}I -glucagon bound to human glucagon receptor in the membranes and excited the scintillant in the WGA beads to light emission. Glucagon or samples binding to the receptor competed with ^{125}I -glucagon.

30 All steps in the membrane preparation were kept on ice or performed at 4°C. BHK cells were harvested and centrifuged. The pellet was resuspended in homogenisation buffer (25 mM HEPES pH = 7.4, 2.5 mM $CaCl_2$, 1.0 mM $MgCl_2$, 250 mg/L bacitracin), homogenised 2 x 10 sec using Polytron 10-35 homogenizer (Kinematica) and added the same amount of homogenisation buffer as used for resuspension. After centrifugation (15 min at 1000 x g) the su-
35 pernatant was transferred to cold centrifuge tubes and centrifuged for 45 min at 40.000 x g.

The pellet was resuspended in homogenisation buffer, homogenised 2 x 10 sec (Polytron) and additional homogenisation buffer was added. The suspension was centrifuged for 45 min at 40.000 x g and the pellet was resuspended in resuspension buffer (25 mM HEPES pH = 7.4, 2.5 mM CaCl₂, 1.0 mM MgCl₂) and homogenised 2 x 10 sec. (Polytron). The protein concentration was normally around 1.75 mg/mL. Stabilisation buffer (25 mM HEPES pH = 7.4, 2.5 mM CaCl₂, 1.0 mM MgCl₂, 1% BSA, 500 mg/L bacitracin, 2.5 M sucrose) was added and the membrane preparation was stored at -80°C.

The glucagon binding assay was carried out in opti plates (Polystyrene Microplates, Packard). 50 µL assay buffer (25 mM HEPES pH = 7.5, 2.5 mM CaCl₂, 1.0 mM MgCl₂, 0.003% Tween-20, 0.005% bacitracin, 0.05% sodium azide) and 5 µL glucagon or test compound (in DMSO) were added to each well. 50 µL tracer (¹²⁵I-porcine glucagon, 70.000 cpm) and 50 µL membranes (12.5 µg) containing the human glucagon receptor were then added to the wells. Finally 50 µL WGA beads containing 1 mg beads were transferred to the well. The assay was incubated for 4 hours on a shaker and then settled for 8-48 hours. The opti plates were counted in a Topcounter. Non-specific binding was determined with 500 nM of glucagon.

Synthesis methods

The following synthesis protocols refer to intermediate compounds and final products identified in the specification and in the synthetic schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the preparation of the glucagon antagonists of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

Some of the NMR data shown in the following examples are only selected data.

Unless otherwise specified in the examples, the *cis/trans* isomeric compounds were obtained as mixtures of *cis* and *trans* isomers, which may be separated by chromatography. Thus, the present invention comprises the compounds in form of mixtures of *cis* and *trans* isomers as well as the pure isomeric forms.

In the examples the following terms are intended to have the following meanings:

DMF:	<i>N,N</i> -dimethylformamide
DMSO:	dimethyl sulfoxide
Fmoc:	9-fluorenylmethyloxycarbonyl
HBTU:	2-(1 <i>H</i> -Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
M.p.:	melting point
NCS:	<i>N</i> -Chlorosuccinimide
NMP:	<i>N</i> -methylpyrrolidone
-OSu:	2,5-dioxo-pyrrolidin-1-yloxy
TFA:	trifluoroacetic acid
THF:	tetrahydrofuran

The final products obtained were characterized by analytical RP-HPLC (retention time) and/or by HPLC-MS (molecular mass and/or retention time).

The RP-HPLC analyses were performed on a Waters HPLC system consisting of WatersTM 600S Controller, WatersTM 996 Photodiode Array Detector, WatersTM 717 Autosampler, WatersTM 616 Pump, WatersTM 3 mm x 150 mm 3.5 μ C-18 Symmetry column and Millenium QuickSet Control Ver. 2.15 using UV detection at 214 nm. A linear gradient was applied from 5% to 90% acetonitrile/0.1% TFA/water over 15 min at a flow rate of 1 mL/minute.

HPLC-MS (METHOD A):

The following instrumentation was used:

- Sciex API 100 Single quadropole mass spectrometer
- Perkin Elmer Series 200 Quard pump
- Perkin Elmer Series 200 autosampler

- Applied Biosystems 785A UV detector
 - Sedex 55 evaporative light scattering detector
 - A Valco column switch with a Valco actuator controlled by timed events from the pump.
- 5 The Sciex Sample control software running on a Macintosh PowerPC 7200 computer was used for the instrument control and data acquisition.

The HPLC pump was connected to four eluent reservoirs containing:

- A: Acetonitrile
B: Water
C: 0.5 % TFA in water
D: 0.02 M ammonium acetate

10

The requirements for samples are that they contain approximately 500 µg/mL of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)

15

The analysis was performed at room temperature by injecting 20 µL of the sample solution on the column, which was eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions were used.

20

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µL/min (1/50) through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

- 25 The remaining 1.48 mL/min (49/50) was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

30

The LC conditions, detector settings and mass spectrometer settings used for the different

methods are given in the following tables.

Column	Waters Symmetry C ₁₈ 3 mm x 150 mm		
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 15 min at 1 mL/min		
Detection	UV: 214 nm	ELS: 40°C	
MS	Experiment:	Start: 100 amu	Stop: 800 amu Step: 0.2 amu
	Dwell:	0.571 msec	
	Method:	Scan 284 times = 9.5 min	

5 HPLC-MS (METHOD B):

This method was identical to METHOD A but using the following conditions and settings:

Column	YMC ODS-A 120Å s - 5μ 3 mm x 50 mm id		
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 mL/min		
Detection	UV: 214 nm	ELS: 40°C	
MS	Experiment:	Start: 100 amu	Stop: 800 amu Step: 0.2 amu
	Dwell:	0.571 msec	
	Method:	Scan 284 times = 9.5 min	

10 HPLC-MS (METHOD C):

The following instrumentation was used:

- Hewlett Packard series 1100 MSD G1946A Single quadropole mass spectrometer
- Hewlett Packard series 1100 MSD G1312A Bin pump
- Hewlett Packard series 1100 MSD G1313A ALS autosampler
- 15 • Hewlett Packard series 1100 MSD G1315A DAD diode array detector

The HP LC/MSD ChemStation control software running on a HP Vectra computer was used for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

- A: 0.05% TFA in water
B: Acetonitrile

The analysis was performed at room temperature by injecting 1 μ L of the sample solution on
5 the column which was eluted with a gradient of acetonitrile in 0.05% TFA.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Grom Nucleosil 100 C18, 3 μ m, 2 mm x 60 mm
Gradient	10% - 100% acetonitrile in 0.05% TFA linearly during 5.8 min at 0.6 mL/min
Detection	UV: 210 nm (diode array)
MS	Ionisation mode: API-ES Experiment: Start: 100 amu Stop: 1000 amu Step: 0.1 amu

10

HPLC-MS (METHOD D):

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- 15 • Hewlett Packard series 1100 G13 15A DAD diode array detector
- Sciex 300 triplequadropole mass spectrometer
- Gilson 215 micro injector
- Sedex 55 evaporative light scattering detector

20 Pumps and detectors were controlled by MassChrom 1.1.1 software running on a MacIntosh G3 computer. Gilson Unipoint Version 1.90 controls the auto-injector.

The HPLC pump was connected to two eluent reservoirs containing:

- A: 0.01% TFA in water
B: 0.01% TFA in acetonitrile

25

The analysis was performed at room temperature by injecting an appropriate volume of the sample (preferably 1 μ L) onto the column that was eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are:

5

Column	YMC ODS-A 120Å s 5 μ 3 mm X 50 mm id
Gradient	5% - 90% acetonitrile linearly during 7.5 min at 1.5 ml/min
Detection	210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

HPLC-MS (METHOD E):

The following instrumentation was used:

- 10
- Hewlett Packard series 1100 MSD G1946A Single quadropole mass spectrometer
 - Hewlett Packard series 1100 MSD G1312A Bin pump
 - Hewlett Packard series 1100 MSD G1313A ALS autosampler
 - Hewlett Packard series 1100 MSD G1315A DAD diode array detector
- 15
- The HP LC/MSD ChemStation control software running on a HP Vectra computer was udes for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: Acetonitrile

- 20
- The analysis was performed at room temperature by injecting 1 μ L of the sample solution on the column which was eluted with a gradient of acetonitrile in 0.01% TFA.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra 100A MS C-18 3.5 μ m, 2 mm x 50 mm
Gradient	10% - 100% acetonitrile in 0.05% TFA linearly during 4.5 min at 1.5 mL/min
Detection	UV: 210 nm (diode array)
MS	Ionisation mode: API-ES Experiment: Start: 100 amu Stop: 1000 amu Step: 0.1 amu

5

HPLC-MS (Method F):

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- 10 • Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument was controlled by HP Chemstation software.

- 15 The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water
B: 0.01% TFA in acetonitrile

The analysis was performed at 40°C by injecting an appropriate volume of the sample (preferably 1 μ L) onto the column, which was eluted with a gradient of acetonitrile.

- 20 The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id
Gradient	10% - 100% acetonitrile linearly during 7.5 min at 1.0 mL/min
Detection	UV: 210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

The compounds of the present invention may be purified using one of the following HPLC methods:

5 Hit fractionation method I

HPLC purification/fractionation of hits is performed on Nucleosil C-18 7 μ m 8 x 100 mm columns (packed by Grom). A standard gradient with water/acetonitrile added 0.01% TFA is used. Flow rate 9 mL/min starting at 10% organic modifier ending after 18 min on 100% organic modifier. This condition is kept for 1 min. Fractions of 4 mL are collected in a deep well
10 collection plate.

Equipment:

2 Gilson 306 pumps equipped with 25 mL SC pump heads, Gilson 806 manometer and Gilson 811c dynamic mixing chamber. UV detection is performed with Gilson 119 UV/VIS de-
15 tector. Gilson 215 Nebula is used as combined injector and fraction collector.

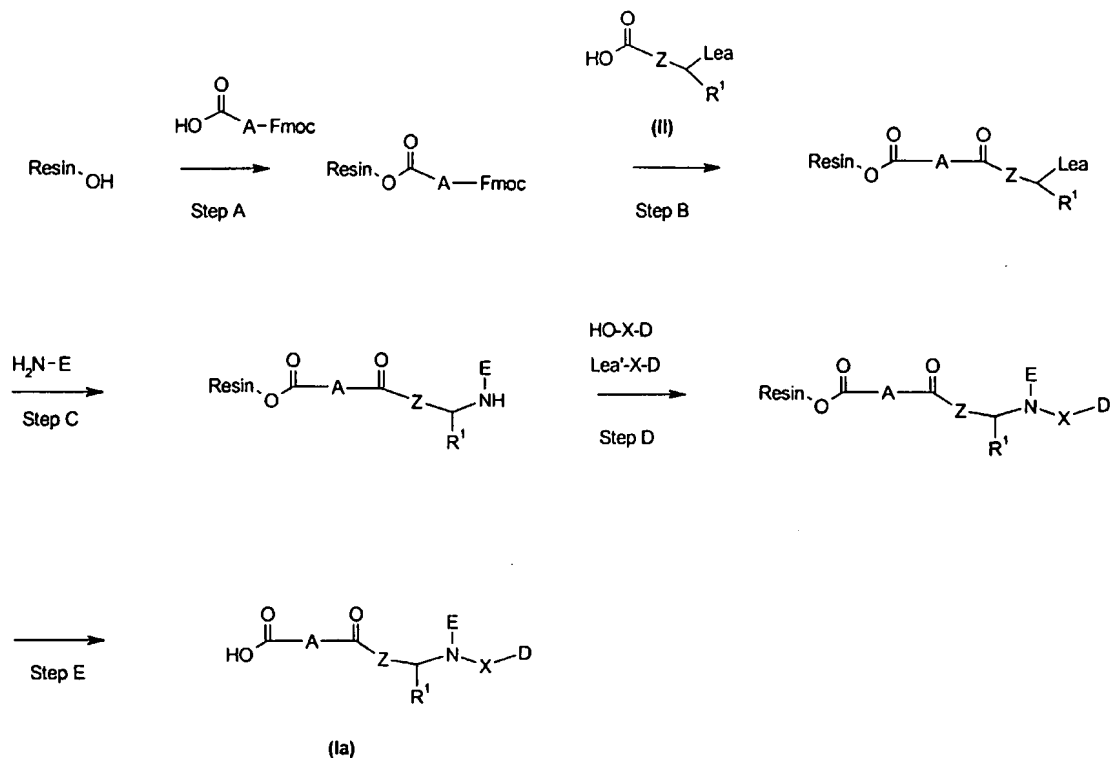
Hit fractionation method II

HPLC purification/fractionation of hits is performed on Waters Xterra columns MS C₁₈ 5 μ m 7.8 x 100 mm columns. A standard gradient with water/acetonitrile added 0.01% TFA is
20 used. Flow rate 15 mL/min starting at 10% organic modifier ending after 11 min on 100% modifier. This condition is kept for 1 min. Fractions of 4 mL are collected in a deep well collection plate.

Equipment:

25 1 Gilson 321 pump equipped with 15 mL H1 pumping heads. UV detection is performed with Gilson 119 UV/VIS detector. Gilson 215 Nebula is used as combined injector and fraction collector.

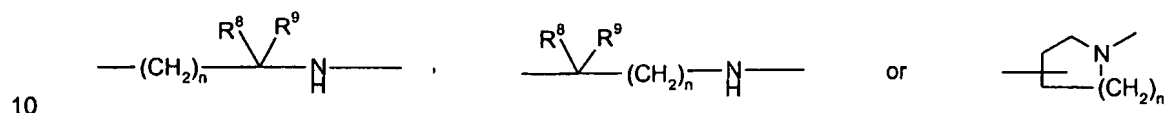
General procedure (A) for the solid phase synthesis of compounds of the general formula (Ia):



5 wherein

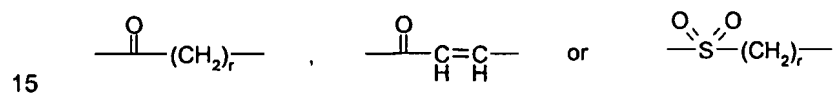
R^1 , Z, E and D are as defined for formula (I),

A is



wherein R^8 and R^9 are as defined for formula (I),

X is



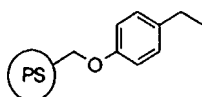
wherein r is as defined for formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

5

Resin denotes a polystyrene resin with a linker such as the Wang linker:



10 wherein PS denotes polystyrene.

Step A:

The reaction is known (Wang S. J., J. Am. Chem. Soc. 95, 1328, 1973) and is generally performed by stirring polystyrene resin loaded with a linker such as the Wang linker with a 4-10 molar excess of Fmoc-protected amino acid activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a catalyst such as *N,N*-4-dimethylaminopyridine. The esterification is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C to 80°C, preferably between 20°C to 40°C. When the esterification is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

20

Step B:

25 *N*-Fluorenylmethyloxycarbonyl protection group is removed by treating the resin bound derivative with a 20%-50% solution of a secondary amine such as piperidine in a polar solvent such as DMF or NMP (Carpino L., Han G., J. Org. Chem. 37, 3404, 1972). The reaction is performed between 20°C and 180°C, preferably between 20°C and 40°C. The deprotection can be quantitated by the absorbance of piperidine-dibenzofulvene adduct released from the resin (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 219). When the reaction is complete excess of reagents is removed by filtration. The resin is successively washed with solvent used in the reaction. The resulting resin bound intermediate is acylated with acid (II). The acylation is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 78) and is generally performed by stirring resin bound intermediate with a 2-5 molar excess of acid (II)

30

activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a side reaction inhibitor such as *N*-hydroxybenzotriazole. The acylation is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C and 80°C, preferably between 20°C and 40°C. When the acylation is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

Step C:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 112) and is generally performed by stirring the resin bound intermediate obtained in step B with a 10-20 molar excess of amine. The nucleophilic displacement is carried out in a solvent such as DMSO, DMF, NMP or a mixture of two or more of these. The reaction is performed between 20°C and 120°C, preferably between 60°C and 80°C. When the reaction is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

Step D:

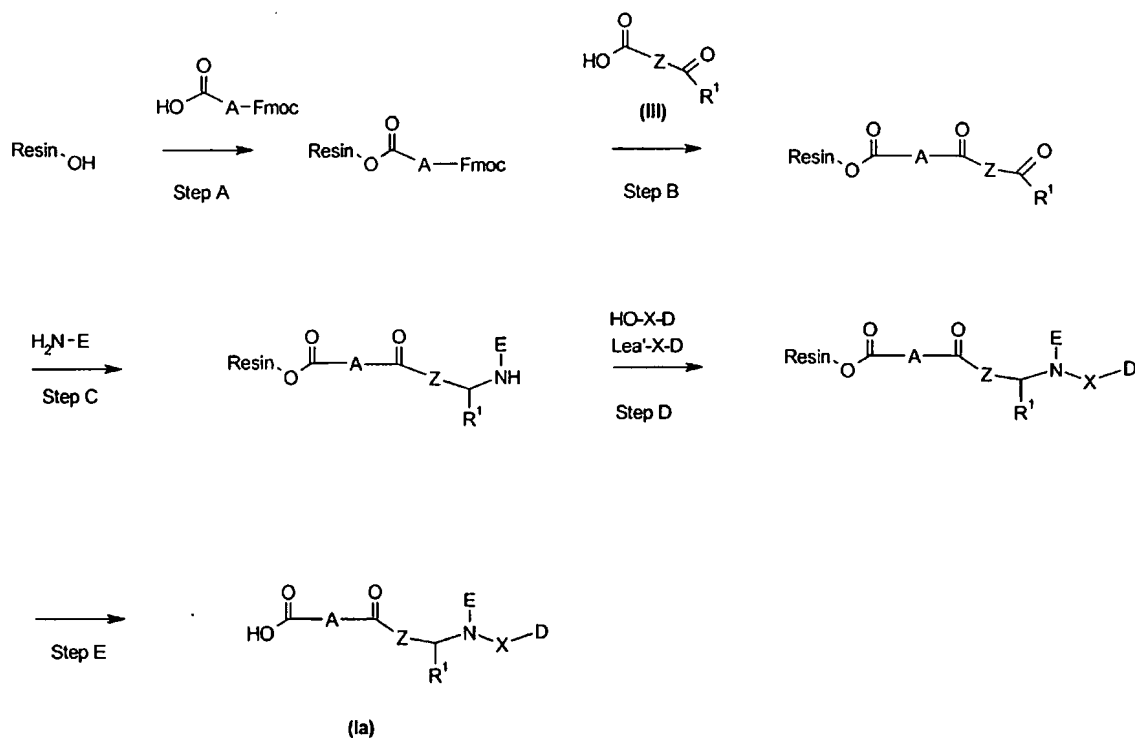
The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 78) and is generally performed by stirring the resin bound intermediate obtained in step C with a 4-10 molar excess of acid HO-X-D activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a catalyst such as pyridine and/or 4-dimethylaminopyridine. The reaction is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete excess of reagents is removed by filtration. Alternatively, a solution of Lea'-X-D in an appropriate solvent such as acetonitrile, toluene, DMF, NMP, THF, dichloromethane, 1,2-dichloroethane or DMSO or a mixture of two or more of these, is added and the mixture is vortexed in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate under heating, if necessary. The resin is successively washed with solvent used in the reaction, followed by washings with dichloromethane.

Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring resin bound intermediate obtained in step D with a 50-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or more of these. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with dichloromethane. The product and washings are collected. The solvent is removed and the product is dried in vacuo. The residue is dissolved in a 1:1 mixture of methanol and dichloromethane (1 mL) and concentrated in vacuo. The product (Ia) is dried in vacuo overnight.

General procedure (B) for the solid phase synthesis of compounds of the general formula (Ia):

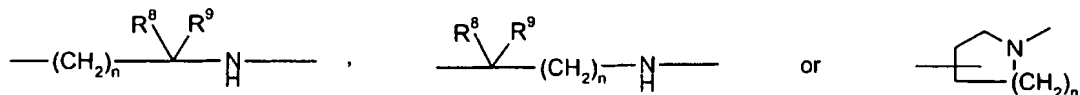
Alternatively, steps B and C of procedure (A) can be modified so that step C is a reductive amination of a resin bound aldehyde or ketone:



20 wherein

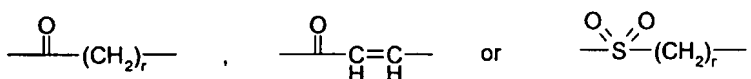
R¹, Z, E and D are as defined for formula (I),

A is



wherein R⁸ and R⁹ are as defined for formula (I),

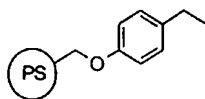
X is



wherein r is as defined for formula (I),

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:



wherein PS denotes polystyrene.

Step B:

This step is identical to step B of general procedure (A) with the modification that acid (III) is used instead of acid (II).

Step C:

The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring resin bound aldehyde or ketone with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. A

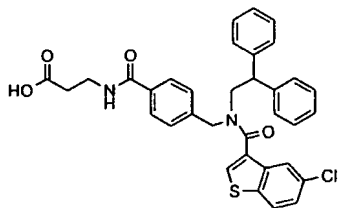
reducing agent such as sodium cyanoborohydride may be used. The reaction is performed between 20°C and 120°C, preferably at 25°C.

The following examples 1 to 9 were prepared according to general procedure (A).

5

EXAMPLE 1 (general procedure (A))

3-(4-([N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino)methyl]benzoyl-amino)propionic acid



10

Step A: Resin bound Fmoc-3-aminopropionic acid

Polystyrene resin loaded with the Wang linker (1.07 mmol/g, 25.0 g, 26.75 mmol) was treated overnight at 25°C with a solution of *N*-Fmoc-3-aminopropionic acid (33.3 g, 107 mmol) in 100 mL THF activated with diisopropylcarbodiimide (8.5 mL, 54 mmol) in the presence of 4-dimethylaminopyridine (0.2 g). Excess of reagents was removed by filtration. The resin bound intermediate was successively washed with 3 x 100 mL THF, 3 x 100 mL DMF and 3 x 100 mL methanol. The resin was dried overnight in vacuo at 50°C for 16 hours to afford 31.54 g resin bound Fmoc-3-aminopropionic acid.

A small sample of resin bound intermediate (25 mg) was withdrawn and treated with 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was diluted with 10 mL acetonitrile and analyzed by HPLC. The yield was calculated from HPLC trace at 214 nm compared to the solution of a standard.

25

Step B: Resin bound 3-[4-(bromomethyl)benzoyl]aminopropionic acid

The above resin bound Fmoc-3-aminopropionic acid (3.95 g, 2.4 mmol) was treated with 40 mL 50% piperidine in DMF for 15 min. The reagent was removed by filtration. The resin was successively washed with 3 x 20 mL DMF and 20 mL of a 1M solution of *N*-hydroxybenzotriazole in DMF. The resulting resin bound intermediate was treated with a solution of 4-bromomethylbenzoic acid (2.15 g, 10 mmol) and *N*-hydroxybenzotriazole (1.52 g, 10 mmol) in 25 mL THF

30

activated by diisopropylcarbodiimide (1.57 mL, 10 mmol). The reaction was performed at 25°C for 12 hours. Excess of reagents was removed by filtration. The resin bound intermediate was successively washed with 3 x 20 mL THF, 3 x 20 mL DMF and 3 x 20 mL methanol. The resin was dried in vacuo at 50°C for 16 hours to afford 3.77 g resin bound 3-[4-(bromo-

5 methyl)benzoyl]aminopropionic acid.

An analytical sample of resin bound intermediate (0.05 g) was withdrawn and treated with 1 mL 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was diluted with 20 mL of acetonitrile and characterized by analytical RP-HPLC (R_t =

10 8.25 min) and by HPLC-MS (Method A) (m/z = 287 ($M + 1$)).

Step C: Resin bound 3-(4-(((N-2,2-diphenylethyl)methyl)benzoyl)amino)propionic acid

The above resin bound 3-[4-(bromomethyl)benzoyl]aminopropionic acid (1.0 g, 0.64 mmol)

15 was treated with 2,2-diphenylethylamine (1.26 g, 6.4 mmol) in 4 mL DMSO. The reaction was stirred at 80°C for 12 hours. Excess of reagents was removed by filtration. The resin was successively washed with 3 x 10 mL DMSO and 3 x 10 mL methanol and dried in vacuo at 50°C for 16 hours to afford 1.07 g resin bound 3-(4-(((N-2,2-

20 diphenylethyl)methyl)benzoyl)amino)propionic acid.

An analytical sample of resin bound intermediate (0.05 g) was withdrawn and treated with 1 mL 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was dissolved in 20 mL of acetonitrile and characterized by analytical RP-HPLC (R_t =

25 8.70 min) and by HPLC-MS (Method A) (m/z = 417 ($M + 1$)).

Step D: Resin bound 3-(4-([N-(5-chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino]methyl)benzoylamino)propionic acid

The above resin bound 3-(4-(((N-2,2-diphenylethyl)methyl)benzoyl)amino)propionic acid (1.02 g, 0.61 mmol) was suspended in THF and successively washed with 2 x 10 mL THF, 2 x 10 mL 5% diisopropylethylamine in THF and 5 x 10 mL THF. The resin slurry was then treated with 5-chlorobenzo[b]thiophen-3-carboxylic acid (0.51 g, 2.4 mmol) in 4 mL THF, 4 mL pyridine, diisopropylcarbodiimide (0.19 mL, 1.2 mmol) and 4-dimethylaminopyridine (24 mg, 0.12 mmol). The reaction mixture was stirred at 25°C for 12 hours. The resin was drained and

30

successively washed with 3 x 10 mL THF, 3 x 10 mL DMF and 5 x 10 mL dichloromethane and used in next step without any characterization.

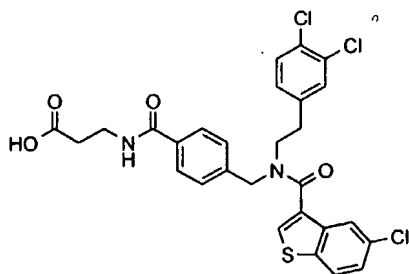
Step E: 3-(4-([N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino]methyl)-benzoylamino)propionic acid

The resin bound 3-(4-([N-(5-chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)-amino]methyl)benzoylamino)propionic acid was treated with a 50% solution of TFA in dichloromethane (10 mL). The cleavage mixture was stirred for 45 min at 25°C. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was dissolved in a 1:1 mixture of methanol and dichloromethane (1 mL) and concentrated in vacuo to afford 0.359 g of the title compound. The product was characterized by analytical RP-HPLC ($R_t = 14.2$ min) and by HPLC-MS (Method A) ($m/z = 597$ ($M + 1$)).

The crude product (50 mg) was purified by column chromatography on RP-C18 silica gel (Sep-Pak, Waters) eluting with a mixture of acetonitrile and water. Pure fractions were pooled and evaporated in vacuo to afford 16.7 mg of pure title compound.

EXAMPLE 2 (general procedure (A))

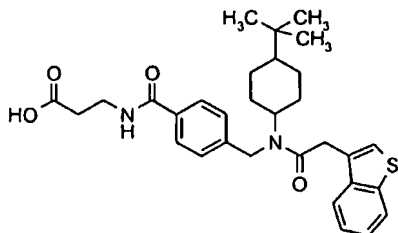
3-(4-([N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(3,4-dichlorophenylethyl)amino]methyl)-benzoylamino)propionic acid



The product was characterized by analytical RP-HPLC ($R_t = 14.12$ min) and by HPLC-MS (Method A) ($m/z = 589$ ($M + 1$)).

EXAMPLE 3 (general procedure (A))

3-(4-({N-(2-Benzo[b]thiophen-3-yl-acetyl)-N-(4-*tert*-butylcyclohexyl)amino}methyl)benzoyl-amino)propionic acid

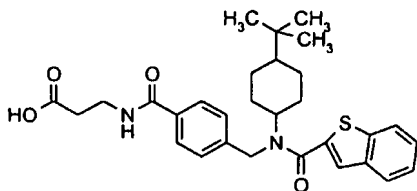


5

The product was characterized by analytical RP-HPLC ($R_t = 14.96$ min) and by HPLC-MS (Method A) ($m/z = 535$ ($M + 1$)).

EXAMPLE 4 (general procedure (A))

10 3-(4-({N-(Benzo[b]thiophen-2-carbonyl)-N-(4-*tert*-butylcyclohexyl)amino}methyl)benzoyl-amino)propionic acid

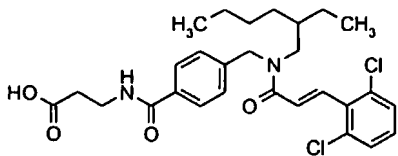


15

The product was characterized by analytical RP-HPLC ($R_t = 15.17$ min) and by HPLC-MS (Method A) ($m/z = 521$ ($M + 1$)).

EXAMPLE 5 (general procedure (A))

3-(4-({N-[3-(2,6-Dichlorophenyl)acryloyl]-N-(2-ethylhexyl)amino}methyl)benzoylamino)-propionic acid

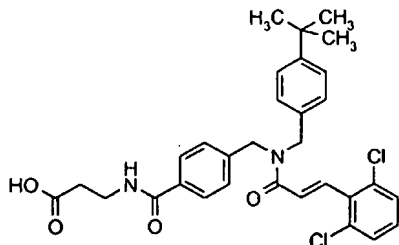


20

The product was characterized by analytical RP-HPLC ($R_t = 15.26$ min) and by HPLC-MS (Method A) ($m/z = 533$ ($M + 1$)).

EXAMPLE 6 (general procedure (A))

3-(4-{{N-[3-(2,6-Dichlorophenyl)acryloyl]-N-(4-*tert*-butylbenzyl)amino]methyl}benzoylamino)-propionic acid

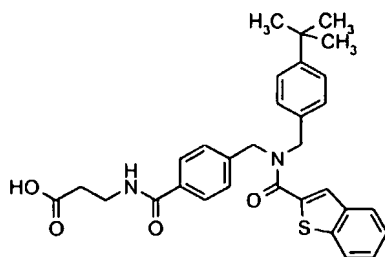


5

The product was characterized by analytical RP-HPLC ($R_t = 15.08$ min) and by HPLC-MS (Method A) ($m/z = 567$ ($M + 1$)).

EXAMPLE 7 (general procedure (A))

10 3-(4-{{N-(Benzo[b]thiophen-2-carbonyl)-N-(4-*tert*-butylbenzyl)amino]methyl}benzoylamino)-propionic acid

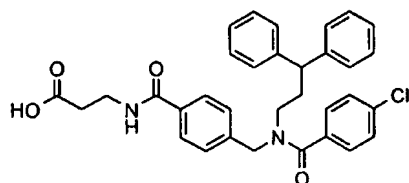


15

The product was characterized by analytical RP-HPLC ($R_t = 14.70$ min) and by HPLC-MS (Method A) ($m/z = 529$ ($M + 1$)).

EXAMPLE 8 (general procedure (A))

3-(4-{{N-(4-Chlorobenzoyl)-N-(3,3-diphenylpropyl)amino]methyl}benzoylamino)propionic acid

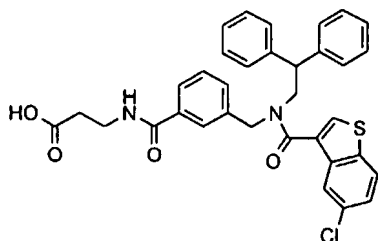


20

The product was characterized by analytical RP-HPLC ($R_t = 13.6$ min) and by HPLC-MS (Method A) ($m/z = 555$ ($M + 1$)).

EXAMPLE 9 (general procedure (A))

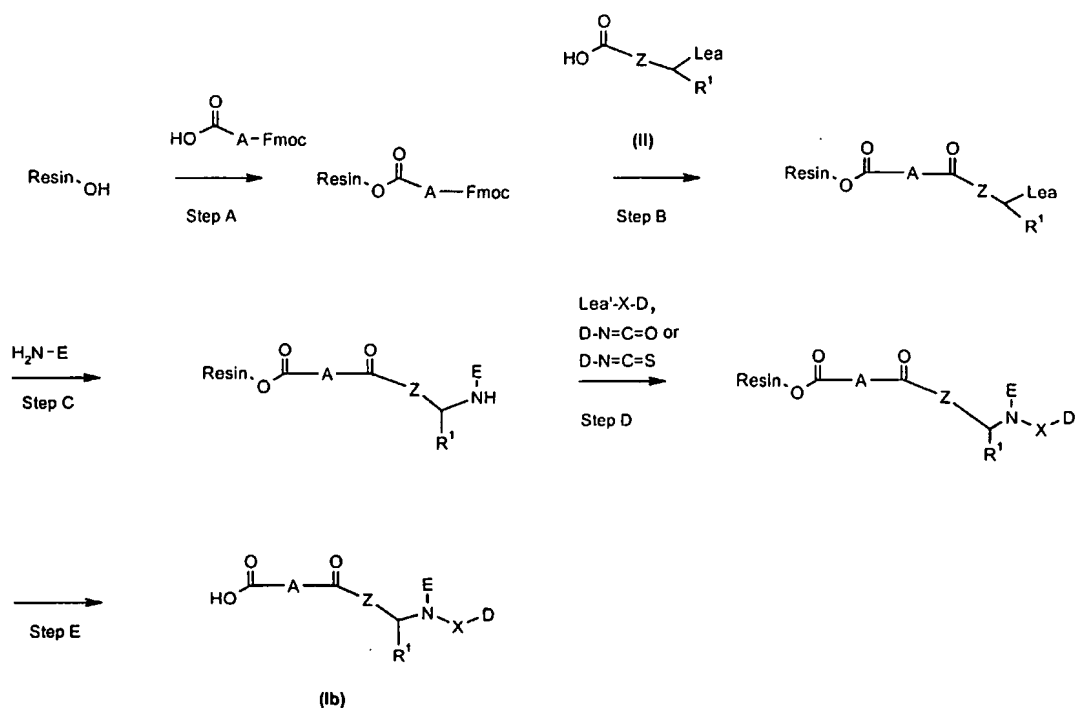
3-(3-({N-(5-Chlorobenzo[b]thiophene-3-carbonyl)-N-(2,2-diphenylethyl)amino)methyl}-benzoylamino)propionic acid



5

The product was characterized by analytical RP-HPLC ($R_t = 14.5$ min) and by HPLC-MS (Method A) ($m/z = 597$ ($M + 1$)).

10 General procedure (C) for the solid phase synthesis of compounds of the general formula (Ib):



wherein

15

A, Z, R^1 , E and D are as defined for formula (I),

X is $-S(O)_2-(CH_2)_r-$, $-C(O)NH-$ or $-C(S)NH-$, wherein r is as defined for formula (I),

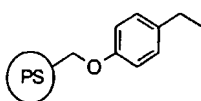
Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

5

Lea' is a leaving group such as $-OSu$, chloro, phenoxy or 4-nitrophenoxy, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:

10



wherein PS denotes polystyrene.

Step A:

- 15 Wang resin (10.0 g, Bachem 1250, 0.96 mmol/g) is suspended in NMP (100 mL) and drained, resuspended in THF (100 mL) and drained again. A solution of a Fmoc-protected amino acid (eg Fmoc- β -alanine) (58 mmol), diisopropylcarbodiimide (4.2 g, 34 mmol) and 4-dimethylaminopyridine (0.07 g, 0.6 mmol) in THF (80 mL) is added to the resin and vortexed for 16 hours. The resin is drained and washed with THF (3 x 100 mL) and NMP (3 x 20 100 mL).

Step B:

- All the resin synthesised in step A is used in this step. A solution of 20% piperidine in NMP (100 mL) is added to the resin and the mixture vortexed for 1 hour. After draining the resin is 25 washed in NMP (3 x 100 mL) and THF (5 x 100 mL). A solution of intermediate (II), eg 4-(bromomethyl)benzoic acid (or a substituted analogue thereof) (29 mmol), hydroxybenzotriazole (4.4 g, 29 mmol) and diisopropylcarbodiimide (3.6 g, 29 mmol) in THF (70 mL) is added and the mixture is vortexed for 16 hours. The resin is drained and washed with THF (2 x 100 mL), NMP (2 x 100 mL), dichloromethane (2 x 100 mL) and methanol (5 x 100 mL), 30 and dried in vacuo.

Step C:

6 g of the resin synthesised in step B is used in this step. A solution of a primary amine (eg 2-phenethylamine or 4-*tert*-butylcyclohexylamine) (48 mmol) in DMSO is added to the resin

and vortexed at 80°C for 16 hours. The resin is drained and washed with NMP (3 x 100 mL), dichloromethane (3 x 100 mL) and methanol (4 x 100 mL), and dried in vacuo.

Step D:

- 5 50 mg of the resin produced in step C is used in this step. The resin is suspended in NMP (1.5 mL) and drained. A solution of an isothiocyanate or an isocyanate (eg phenylisocyanate or 4-trifluoromethoxyphenylisocyanate) (0.24 mmol) in NMP (1 mL) is added and the mixture is vortexed for 16 hours. Alternatively, a solution of Lea'-X-D in an appropriate solvent such as acetonitrile, toluene, DMF, NMP, THF, dichloromethane, 1,2-dichloroethane or DMSO or
- 10 a mixture of two or more of these, is added and the mixture is vortexed in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate under heating, if necessary. The resin is drained and washed with DMF (3 x 1 mL), methanol (3 x 1 mL), 2-propanol (3 x 1 mL), *tert*-butyl-methylether (3 x 1 mL) and dichloromethane (3 x 1 mL).

15

Step E:

All the resin synthesised in step D is used. A solution of TFA and dichloromethane (1:1, 2 mL) is added to the resin and vortexed for 45 min. The resin is drained and the eluent evaporated in vacuo to give a compound of general formula (Ib).

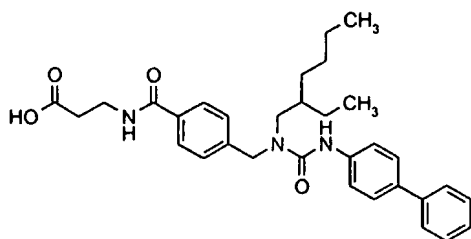
20

Optionally, the compound can be purified by chromatography eg HPLC.

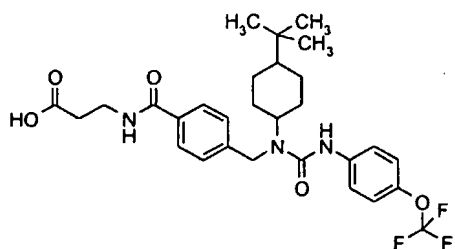
- The compounds of general formula (Ib) can be prepared either as single compounds or by parallel synthesis using the protocol mentioned above in a combinatorial approach. Thousands of
- 25 compounds of formula (Ib) can thus be prepared by this combinatorial approach which can be semi-automated or fully automated. The automation of this protocol can be performed eg using a 96 well setup using an automated synthesizer device.

30

The following examples were prepared according to general procedure (C).

EXAMPLE 10 (general procedure (C))3-{4-[3-Biphenyl-4-yl-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method C): $R_t = 4.30$ min, $m/z = 530$ ($M + 1$).

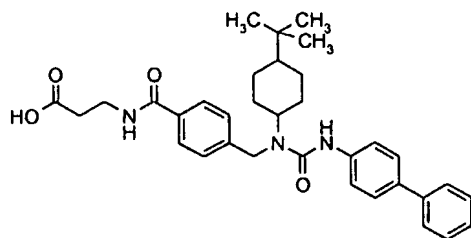
EXAMPLE 11 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

10

The product was characterized by HPLC-MS (Method C): $R_t = 4.33$ min, $m/z = 564$ ($M + 1$).

EXAMPLE 12 (general procedure (C))

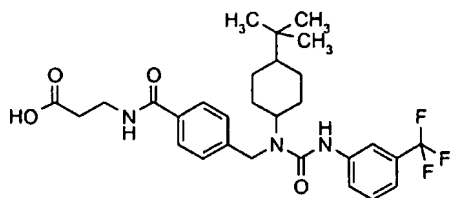
- 15 3-{4-[3-Biphenyl-4-yl-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid



The product was characterized by HPLC-MS (Method C): $R_t = 4.40$ min, $m/z = 556$ ($M + 1$).

EXAMPLE 13 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid

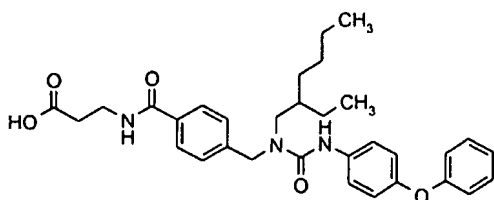


5

The product was characterized by HPLC-MS (Method C): $R_t = 4.31$ min, $m/z = 548$ ($M + 1$).

EXAMPLE 14 (general procedure (C))

3-{4-[1-(2-Ethylhexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

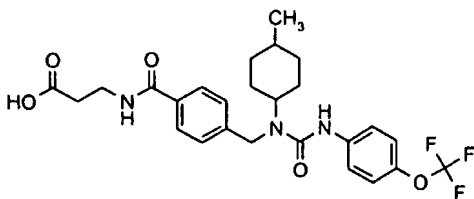


10

The product was characterized by HPLC-MS (Method C): $R_t = 4.30$ min, $m/z = 546$ ($M + 1$).

EXAMPLE 15 (general procedure (C))

15 3-{4-[1-(4-Methylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

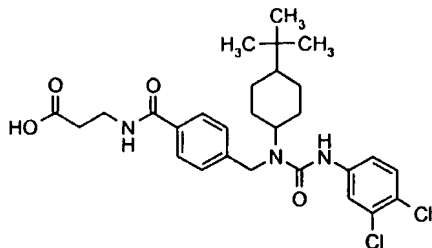


20

The product was characterized by HPLC-MS (Method C): $R_t = 3.78$ min, $m/z = 522$ ($M + 1$).

EXAMPLE 16 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



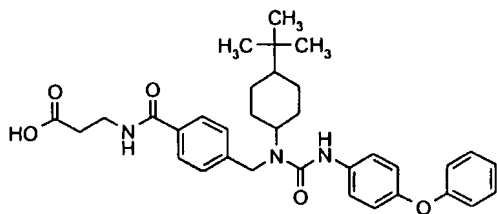
5

The product was characterized by HPLC-MS (Method C): $R_t = 4.62$ min, $m/z = 548$ ($M + 1$).

EXAMPLE 17 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

10

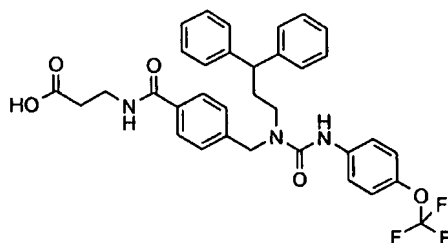


The product was characterized by HPLC-MS (Method C): $R_t = 4.30$ min, $m/z = 572$ ($M + 1$).

15

EXAMPLE 18 (general procedure (C))

3-{4-[1-(3,3-Diphenylpropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

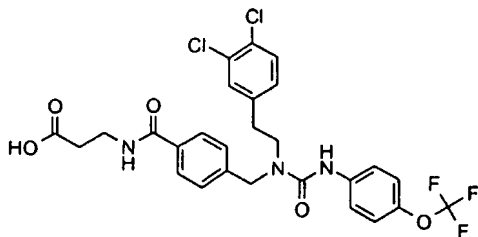


20

The product was characterized by HPLC-MS (Method C): $R_t = 4.13$ min, $m/z = 620$ ($M + 1$).

EXAMPLE 19 (general procedure (C))

3-{4-[1-[2-(3,4-Dichlorophenyl)ethyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid

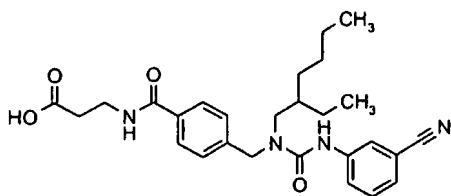


5

The product was characterized by HPLC-MS (Method C): $R_t = 4.00$ min, $m/z = 598$ ($M + 1$).

EXAMPLE 20 (general procedure (C))

3-{4-[3-(3-Cyanophenyl)-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid

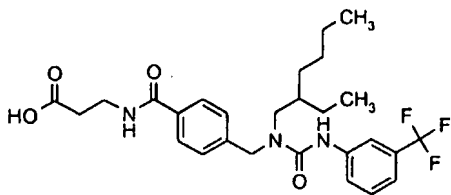


10

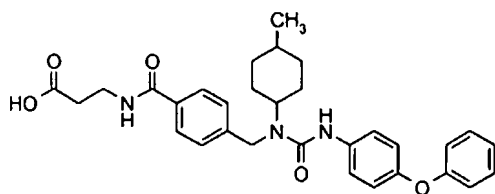
The product was characterized by HPLC-MS (Method B): $R_t = 5.50$ min, $m/z = 479$ ($M + 1$).

EXAMPLE 21 (general procedure (C))

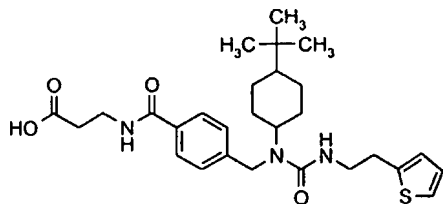
15 3-{4-[1-(2-Ethylhexyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid



The product was characterized by HPLC-MS (Method B): $R_t = 6.17$ min, $m/z = 552$ ($M + 1$).

EXAMPLE 22 (general procedure (C))3-{4-[1-(4-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method B): $R_t = 5.73$ min, $m/z = 530$ ($M + 1$).

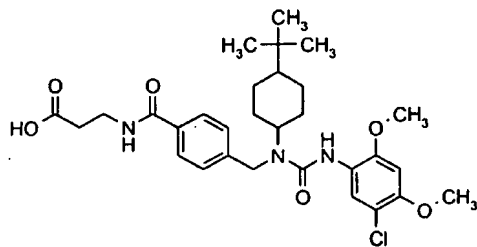
EXAMPLE 23 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-thiophen-2-ylethyl)ureidomethyl]benzoylamino}propionic acid

10

The product was characterized by HPLC-MS (Method B): $R_t = 5.60$ min, $m/z = 514$ ($M + 1$).

EXAMPLE 24 (general procedure (C))

- 15 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(5-chloro-2,4-dimethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

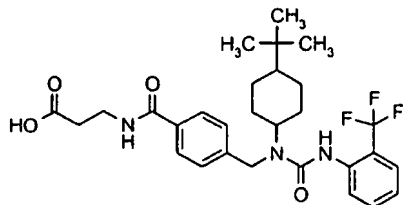


The product was characterized by HPLC-MS (Method B): $R_t = 6.30$ min, $m/z = 574$ ($M + 1$).

20

EXAMPLE 25 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid



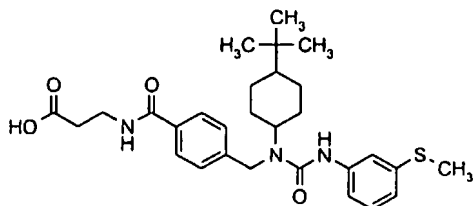
5

The product was characterized by HPLC-MS (Method B): $R_t = 6.10$ min, $m/z = 548$ ($M + 1$).

EXAMPLE 26 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfanylphenyl)ureidomethyl]benzoylamino}-propionic acid

10

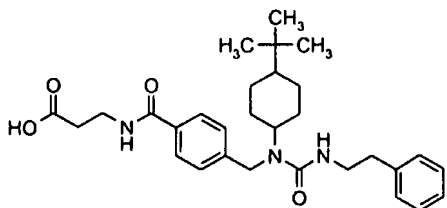


The product was characterized by HPLC-MS (Method B): $R_t = 6.03$ min, $m/z = 526$ ($M + 1$).

15

EXAMPLE 27 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-phenethylureidomethyl]benzoylamino}propionic acid

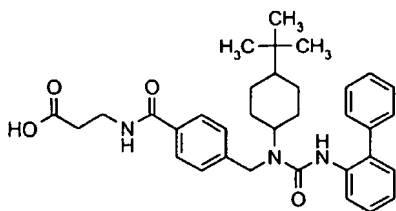


The product was characterized by HPLC-MS (Method B): $R_t = 5.53$ min, $m/z = 508$ ($M + 1$).

20

EXAMPLE 28 (general procedure (C))

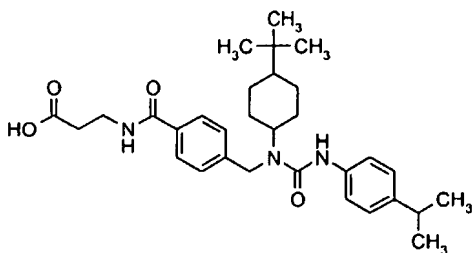
3-{4-[3-Biphenyl-2-yl-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid



- 5 The product was characterized by HPLC-MS (Method B): $R_t = 6.14$ min, $m/z = 556$ ($M + 1$).

EXAMPLE 29 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoyl}aminopropionic acid

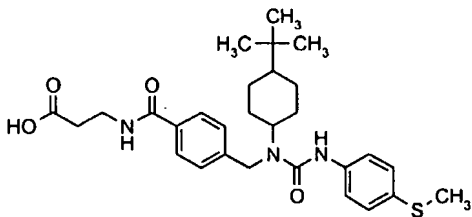


10

The product was characterized by HPLC-MS (Method B): $R_t = 7.98$ min, $m/z = 522$ ($M+1$).

EXAMPLE 30 (general procedure (C))

- 15 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methylsulfanylphenyl)ureidomethyl]benzoyl}amino-propionic acid

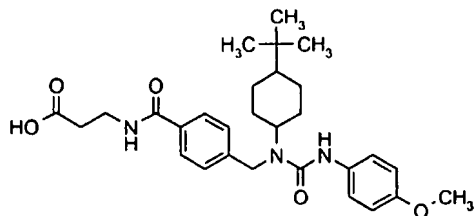


The product was characterized by HPLC-MS (Method B): $R_t = 7.58$ min, $m/z = 526$ ($M+1$).

20

EXAMPLE 31 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methoxyphenyl)ureidomethyl]benzoyl}aminopropionic acid

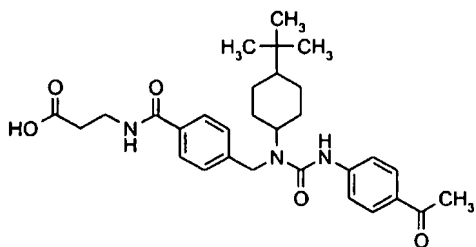


5

The product was characterized by HPLC-MS (Method B): $R_t = 6.93$ min, $m/z = 510$ ($M+1$).

EXAMPLE 32 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-acetylphenyl)ureidomethyl]benzoyl}aminopropionic acid

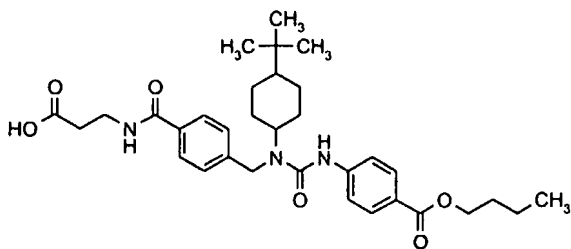


10

The product was characterized by HPLC-MS (Method B): $R_t = 7.03$ min, $m/z = 522$ ($M+1$).

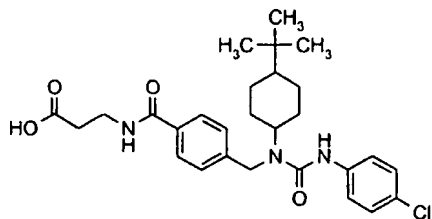
EXAMPLE 33 (general procedure (C))

15 4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid butyl ester

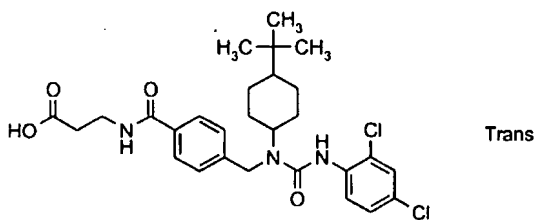


The product was characterized by HPLC-MS (Method B): $R_t = 8.33$ min.

20

EXAMPLE 34 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoyl}aminopropionic acid

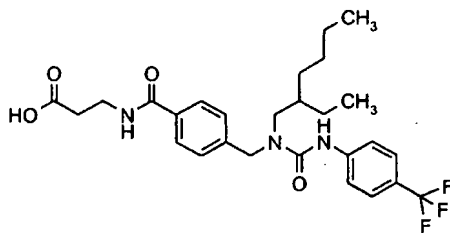
- 5 The product was characterized by HPLC-MS (Method B): $R_t = 7.68$ min, $m/z = 514$ ($M+1$).

EXAMPLE 35 (general procedure (C))3-{4-[1-(4-*trans-tert*-Butylcyclohexyl)-3-(2,4-dichlorophenyl)ureidomethyl]benzoyl}amino}-propionic acid

10

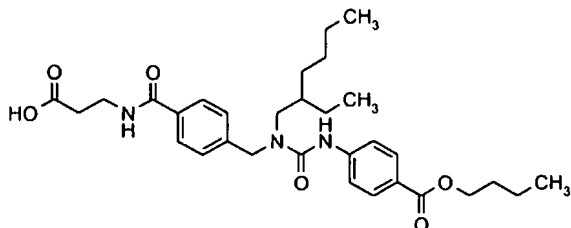
^1H NMR ($\text{DMSO}-d_6$): δ 0.82 (9H, s), 0.9-1.7 (9H, m), 4.04 (1H, t), 4.60 (2H, s), 7.38 (4H, m), 7.60 (2H, m), 7.78 (2H, d), 8.48 (1H, t).

- 15 HPLC-MS (Method B): $R_t = 8.25$ min, $m/z = 548$ ($M+1$).

EXAMPLE 36 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-trifluoromethylphenyl)ureidomethyl]benzoyl}amino}propionic acid

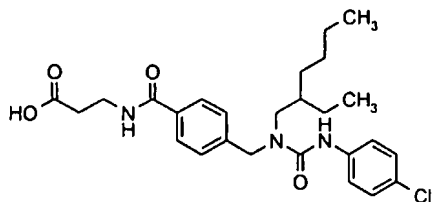
20

^1H NMR ($\text{DMSO}-d_6$): δ 7.33 (2H, d), 7.59 (2H, d), 7.68 (2H, d), 7.81 (2H, d), 8.50 (1H, t), 8.81 (1H, s).

EXAMPLE 37 (general procedure (C))**4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-ethylhexyl)ureido]benzoic acid butyl ester**

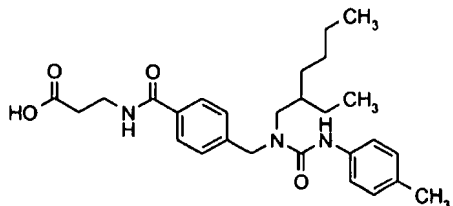
5

^1H NMR (DMSO- d_6): δ 4.23 (2H, t), 4.69 (2H, s), 7.33 (2H, d), 7.60 (2H, d), 7.80 (2H, d), 7.84 (2H, d), 8.49 (1H, bt), 8.81 (1H, s).

EXAMPLE 38 (general procedure (C))**3-{4-[3-(4-Chlorophenyl)-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid**

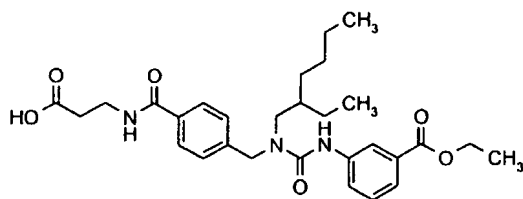
^1H NMR (DMSO- d_6): δ 4.64 (2H, s), 7.04 (2H, d), 7.3-7.35 (4H, m), 7.81 (2H, d), 8.28 (1H, s), 8.48 (1H, bt).

15

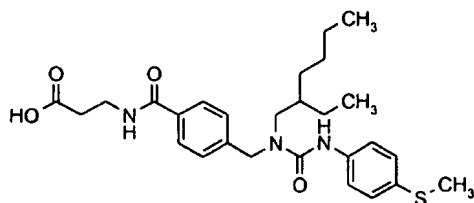
EXAMPLE 39 (general procedure (C))**3-{4-[1-(2-Ethylhexyl)-3-p-tolylureidomethyl]benzoylamino}propionic acid**

^1H NMR (DMSO- d_6): δ 4.65 (2H, s), 7.06 (2H, d), 7.31-7.33 (4H, m), 7.81 (2H, d), 8.29 (1H, s), 8.49 (1H, bt).

20

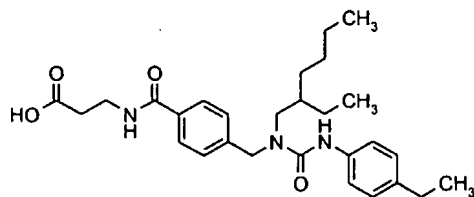
EXAMPLE 40 (general procedure (C))3-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-ethylhexyl)ureido]benzoic acid ethyl ester

- 5 ^1H NMR ($\text{DMSO}-d_6$): δ 4.30 (2H, q), 4.67 (2H, s), 7.33 (2H, d), 7.36 (1H, t), 7.53 (1H, t), 7.74 (1H, bd), 7.80 (2H, d), 8.07 (1H, s), 8.48 (1H, bt), 8.65 (1H, s).

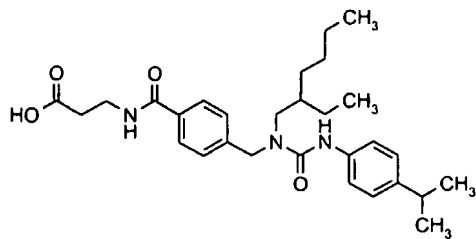
EXAMPLE 41 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-methylsulfonylphenyl)ureidomethyl]benzoylamino}propionic acid

10

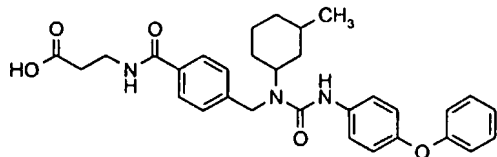
- ^1H NMR ($\text{DMSO}-d_6$): δ 4.66 (2H, s), 7.18 (2H, d), 7.31 (2H, d), 7.39 (2H, d), 7.78 (2H, d), 8.40 (1H, s), 8.50 (1H, bt).

EXAMPLE 42 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-ethylphenyl)ureidomethyl]benzoylamino}propionic acid

- 15 ^1H NMR ($\text{DMSO}-d_6$): δ 4.51 (2H, s), 7.10 (2H, d), 7.32 (4H, m), 7.79 (2H, d), 8.28 (1H, s),
20 8.48 (1H, t).

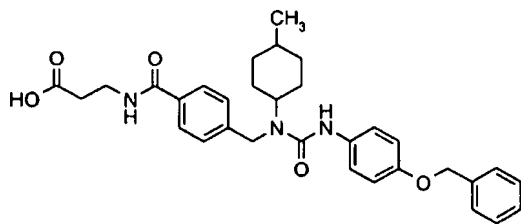
EXAMPLE 43 (general procedure (C))**3-{4-[1-(2-Ethylhexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid**

- 5 ^1H NMR (DMSO- d_6): δ 4.70 (2H, s), 7.33 (2H, d), 7.58 (2H, d), 7.67 (2H, d), 7.78 (2H, d), 8.46 (1H, t), 8.70 (1H, d).

EXAMPLE 44 (general procedure (C))**3-{4-[1-(3-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid**

10

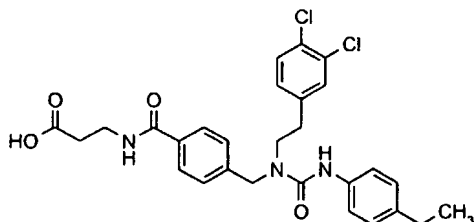
- ^1H NMR (DMSO- d_6): δ 4.61 (2H, s), 6.92 (4H, m), 7.07 (1H, t), 7.33 (4H, m), 7.41 (2H, m), 7.76 (2H, d), 8.29 (1H, d), 8.45 (1H, t).

EXAMPLE 45 (general procedure (C))**3-{4-[3-(4-Benzoyloxyphenyl)-1-(4-methylcyclohexyl)ureidomethyl]benzoylamino}propionic acid**

- 20 ^1H NMR (DMSO- d_6): δ 5.01 (2H, s), 6.90 (2H, d), 7.1-7.3 (10H, m), 7.77 (2H, d), 8.15 (1H, s), 8.44 (1H, bt).

EXAMPLE 46 (general procedure (C))

3-{4-[1-[2-(3,4-Dichlorophenyl)ethyl]-3-(4-ethylphenyl)ureidomethyl]benzoylamino}propionic acid

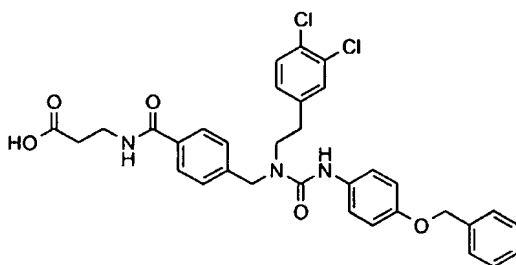


5

¹H NMR (DMSO-*d*₆): δ 4.67 (2H, s), 7.08 (2H, d), 7.25 (1H, d), 7.35 (4H, m), 7.53 (2H, m), 7.81 (2H, d), 8.31 (1H, s), 8.48 (1H, bt).

EXAMPLE 47 (general procedure (C))

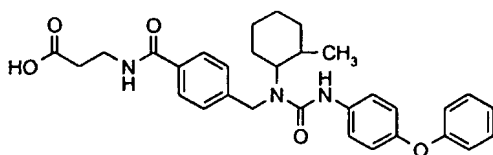
10 3-{4-[3-(4-Benzoyloxyphenyl)-1-[2-(3,4-dichlorophenyl)ethyl]ureidomethyl]benzoylamino}-propionic acid



15 ¹H NMR (DMSO-*d*₆): δ 4.60 (2H, s), 5.10 (2H, s), 6.92 (2H, d), 7.25-7.47 (10H, m), 7.55 (2H, m), 7.25 (1H, d), 7.81 (2H, d), 8.27 (1H, s), 8.45 (1H, t).

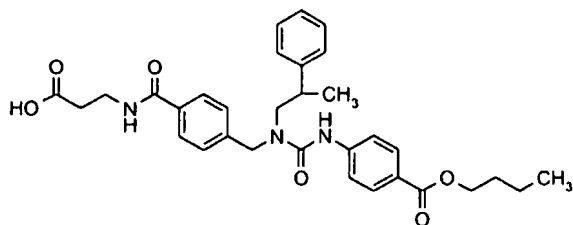
EXAMPLE 48 (general procedure (C))

3-{4-[1-(2-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

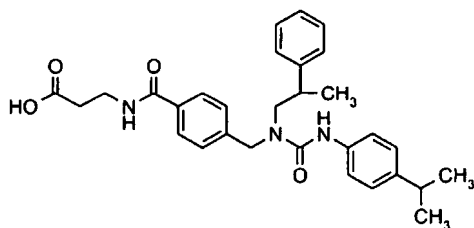


20

HPLC-MS (Method C): *m/z*: 530, *R*_t = 6.96 min.

EXAMPLE 49 (general procedure (C))**4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-phenylpropyl)ureido]benzoic acid butyl ester**

- 5 ^1H NMR (DMSO- d_6): δ 7.20 (2H, t), 7.3 (6H, m), 7.55 (2H, d), 7.77 (2H, d), 7.83 (2H, d), 8.46 (1H, d), 8.69 (1H, s).

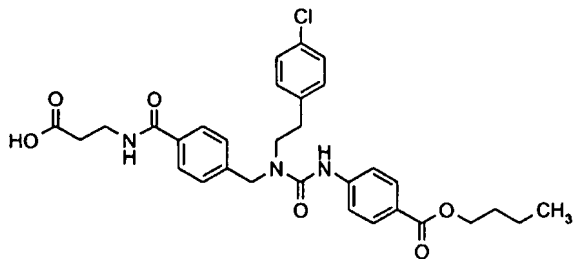
EXAMPLE 50 (general procedure (C))**3-{4-[3-(4-Isopropylphenyl)-1-(2-phenylpropyl)ureidomethyl]benzoylamino}propionic acid**

10

- ^1H NMR (DMSO- d_6): δ 7.11 (2H, d), 7.2-7.35 (9H, m), 7.78 (2H, d), 8.23 (1H, s), 8.49 (1H, t).

EXAMPLE 51 (general procedure (C))

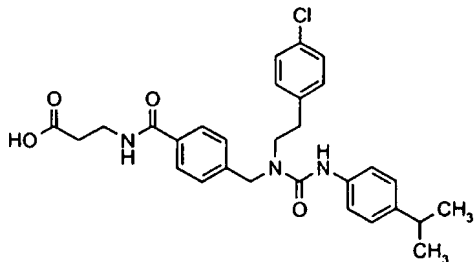
- 15 **4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-[2-(4-chlorophenyl)ethyl]ureido]benzoic acid butyl ester**



- 20 ^1H NMR (DMSO- d_6): δ 7.27 (2H, d), 7.31-7.36 (4H, m), 7.60 (2H, d), 7.81 (2H, d), 7.86 (2H, d), 8.47 (1H, t), 8.77 (1H, s).

EXAMPLE 52 (general procedure (C))

3-{4-[1-[2-(4-Chlorophenyl)ethyl]-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

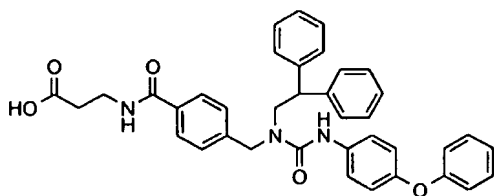


5

¹H NMR (DMSO-*d*₆): δ 7.10 (2H, d), 7.24 (2H, d), 7.30-7.34 (6H, m), 7.78 (2H, d), 8.29 (1H, s).

EXAMPLE 53 (general procedure (C))

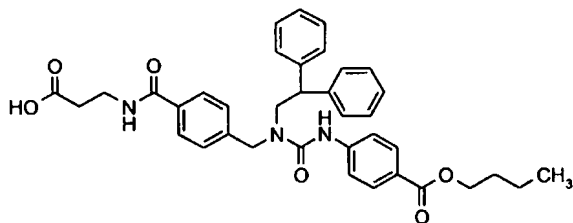
10 3-{4-[1-(2,2-Diphenylethyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid



HPLC-MS (Method C): *m/z* 614, *R*_t = 7.35 min.

15 EXAMPLE 54 (general procedure (C))

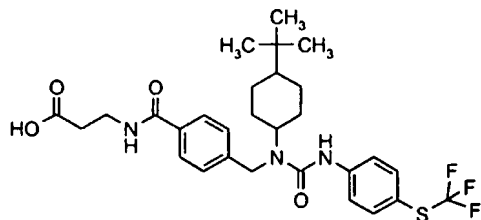
4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2,2-diphenylethyl)ureido]benzoic acid butyl ester



20 ¹H NMR (DMSO-*d*₆): δ 7.18 (2H, t), 7.25-7.3 (6H, m), 7.34 (4H, m), 7.47 (2H, d), 7.75 (2H, d), 7.80 (2H, d), 8.52 (1H, b), 8.71 (1H, s).

EXAMPLE 58 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]-benzoylamino}propionic acid

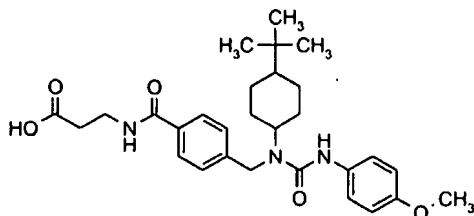


5

^1H NMR (DMSO- d_6): δ 8.46 (s, 1H); 8.34 (s, 1H); 7.74 (d, 2H); 7.40 (d, 2H); 7.34 (d, 2H); 7.16 (d, 2H); 4.59 (s, 2H); 0.85 (s, 9H).

10 **EXAMPLE 59 (general procedure (C))**

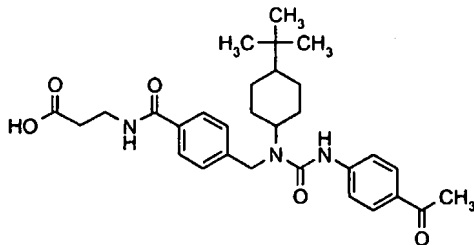
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methoxyphenyl)ureidomethyl]benzoylamino}propionic acid



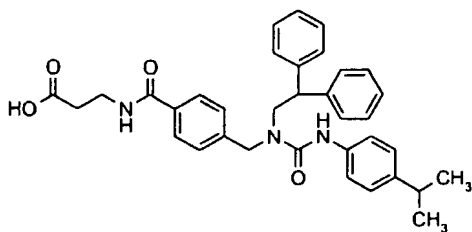
15 ^1H NMR (DMSO- d_6): δ 8.46 (s, 1H); 8.18 (s, 1H); 7.76 (d, 2H); 7.30 (d, 2H); 7.28 (d, 2H); 6.8 (d, 2H); 4.58 (s, 2H); 3.73 (s, 3H); 0.80 (s, 9H).

EXAMPLE 60 (general procedure (C))

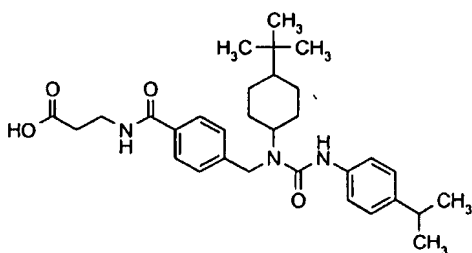
3-{4-[3-(4-Acetylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid



20

EXAMPLE 55 (general procedure (C))**3-{4-[1-(2,2-Diphenylethyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid**

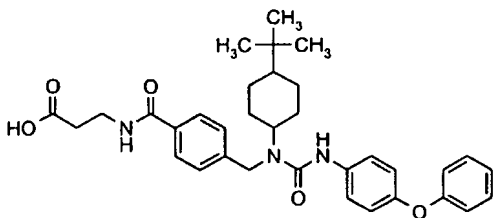
5 ^1H NMR (DMSO- d_6): δ 7.06 (2H, d), 7.16-7.35 (14H, m), 7.75 (2H, d), 8.24 (1H, s).

EXAMPLE 56 (general procedure (C))**3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid**

10

^1H NMR (DMSO- d_6): δ 8.41 (s, 1H); 8.20 (s, 1H); 7.75 (d, 2H); 7.34 (d, 2H); 7.32 (d, 2H); 7.08 (d, 2H); 4.08 (s, 2H); 1.19 (d, 6H); 0.83 (s, 9H).

15 **EXAMPLE 57 (general procedure (C))**

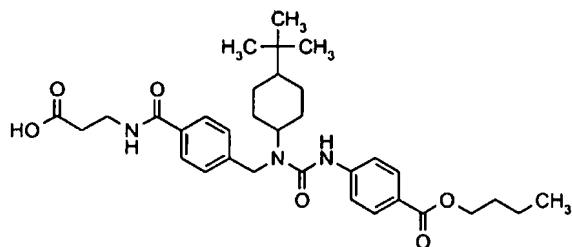
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

20 ^1H NMR (DMSO- d_6): δ 8.44 (s, 1H); 8.35 (s, 1H); 7.78 (d, 2H); 7.45 (d, 2H); 7.38 (d, 2H); 7.34 (d, 2H); 6.94 (m, 5H); 4.60 (s, 2H); 0.81 (s, 9H).

¹H NMR (DMSO-*d*₆): δ 8.70 (s, 1H); 8.42 (s, 1H); 7.86 (d, 2H); 7.76 (d, 2H); 7.62 (d, 2H); 7.30 (d, 2H); 4.62 (s, 2H); 0.81 (s, 9H).

EXAMPLE 61 (general procedure (C))

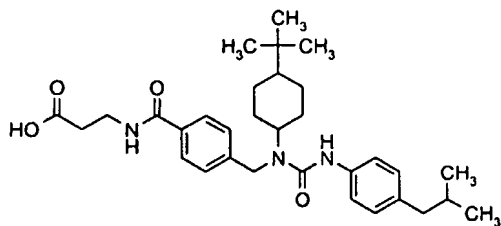
- 5 4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid butyl ester



- 10 ¹H NMR (DMSO-*d*₆): δ 8.71 (s, 1H); 8.42 (t, 1H); 7.83 (d, 2H); 7.76 (d, 2H); 7.61 (s, 2H); 7.32 (d, 2H); 4.64 (s, 2H); 4.26 (t, 2H); 0.94 (t, 3H); 0.83 (s, 9H).

EXAMPLE 62 (general procedure (C))

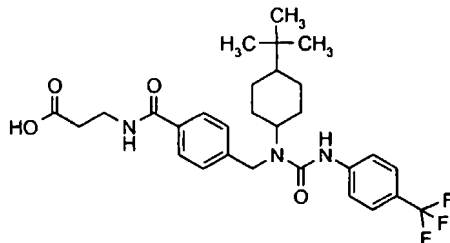
- 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isobutylphenyl)ureidomethyl]benzoylamino}propionic acid



- 15 ¹H NMR (DMSO-*d*₆): δ 8.46 (t, 1H); 8.22 (s, 1H); 7.75 (d, 2H); 7.35 (d, 2H); 7.33 (d, 2H); 7.05 (d, 2H); 4.60 (s, 2H); 1.17 (d, 6H); 0.83 (s, 9H).

EXAMPLE 63 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid

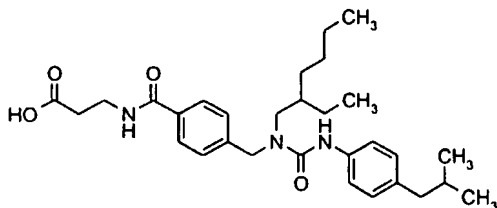


5

^1H NMR (DMSO- d_6): δ 8.72 (s, 1H); 8.45 (t, 1H); 7.78 (d, 2H); 7.72 (d, 2H); 7.60 (d, 2H); 7.35 (d, 2H); 4.65 (s, 2H); 4.10 (m, 1H); 0.85 (s, 9H).

EXAMPLE 64 (general procedure (C))

10 3-{4-[1-(2-Ethylhexyl)-3-(4-isobutylphenyl)ureidomethyl]benzoylamino}propionic acid

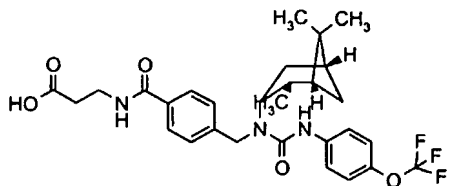


^1H NMR (DMSO- d_6): δ 8.47 (t, 1H); 8.30 (s, 1H); 7.82 (d, 2H); 7.36 (d, 2H); 7.32 (d, 2H); 7.05 (d, 2H); 4.65 (s, 2H); 1.12 (m, 9H); 0.85 (m, 12H).

15

EXAMPLE 65 (general procedure (C))

3-{4-[3-(4-Trifluoromethoxyphenyl)-1-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)ureidomethyl]benzoylamino}propionic acid

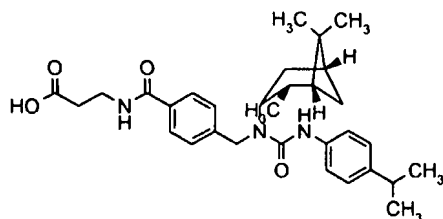


20

^1H NMR (DMSO- d_6): δ 8.52 (s, 1H); 8.44 (t, 1H); 7.81 (d, 2H); 7.52 (d, 2H); 7.35 (d, 2H); 7.22 (d, 2H); 4.91 (m, 1H); 4.76 (s, 2H); 1.22 (s, 3H); 1.13 (s, 3H); 0.98 (d, 3H).

EXAMPLE 66 (general procedure (C))

3-{4-[3-(4-Isopropylphenyl)-1-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)ureidomethyl]benzoylamino}propionic acid

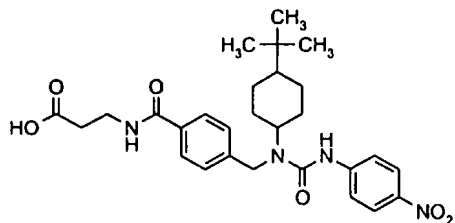


5

^1H NMR (DMSO- d_6): δ 8.44 (s, 1H); 8.17 (t, 1H); 7.78 (d, 2H); 7.34 (d, 2H); 7.26 (d, 2H); 7.08 (d, 2H); 4.93 (m, 1H); 4.72 (s, 2H); 1.22 (s, 3H); 1.18 (d, 6H); 1.13 (s, 3H); 0.98 (d, 3H).

EXAMPLE 67 (general procedure (C))

10 **3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-nitrophenyl)ureidomethyl]benzoylamino}propionic acid**

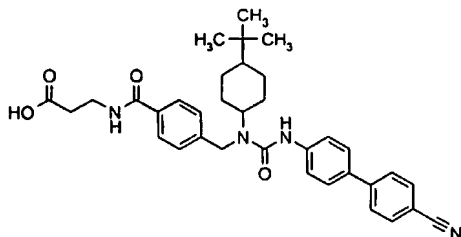


^1H NMR (DMSO- d_6): δ 9.03 (s, 1H); 8.45 (t, 1H); 8.16 (d, 2H); 7.77 (d, 2H); 7.73 (d, 2H); 7.33 (d, 2H); 4.67 (s, 2H); 4.10 (t, 1H); 0.86 (s, 9H).

15

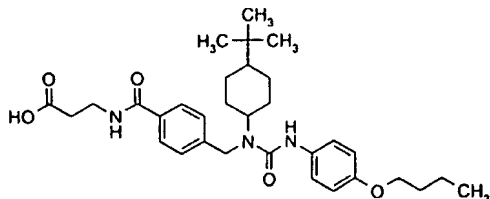
EXAMPLE 68 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4'-cyanobiphenyl-4-yl)ureidomethyl]benzoylamino}-propionic acid



20

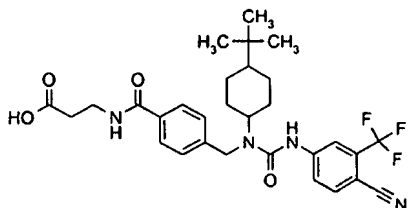
^1H NMR (DMSO- d_6): δ 8.52 (1H, s), 8.48 (1H, t), 7.88 (4H, dd), 7.79 (2H, d), 7.79 (2H, d), 7.62 (2H, d), 7.38 (2H, d).

EXAMPLE 69 (general procedure (C))**3-{4-[3-(4-Butoxyphenyl)-1-(4-*tert*-butyl-cyclohexyl)ureidomethyl]benzoylamino}propionic acid**

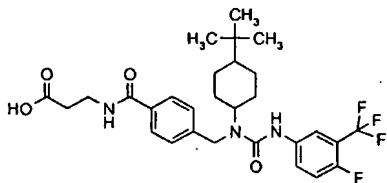
5

¹H NMR (DMSO-*d*₆): δ 8.45 (1H, m), 8.15 (1H, s), 7.78 (2H, d), 7.33 (4H, dd), 6.82 (2H, d).**EXAMPLE 70 (general procedure (C))****3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-cyano-3-trifluoromethylphenyl)ureidomethyl]benzoyl-amino}propionic acid**

10

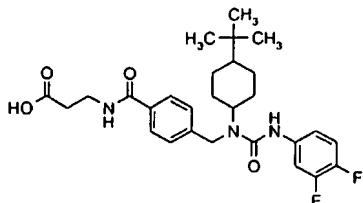
¹H NMR (DMSO-*d*₆): δ 8.43 (1H, m), 8.18 (1H, s), 7.98 (2H, s), 7.75 (2H, d), 7.43 (2H, d).

15

EXAMPLE 71 (general procedure (C))**3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-fluoro-3-trifluoromethylphenyl)ureidomethyl]benzoyl-amino}propionic acid**20 HPLC-MS (method B): *m/z*: 566, *R*_t = 7.95 min.

EXAMPLE 72 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}propionic acid



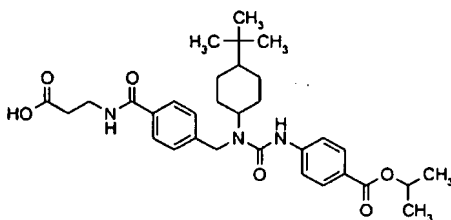
5

HPLC-MS (method B): m/z: 517, R_t = 7.29 min.

EXAMPLE 73 (general procedure (C))

4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid isopropyl ester

10



^1H NMR (DMSO- d_6): δ 8.70 (1H, s), 8.48 (1H, t), 7.83 (2H, d), 7.78 (2H, d), 7.63 (2H, d), 7.32 (2H, d).

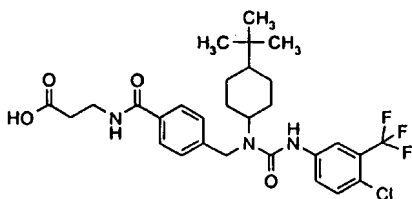
15

HPLC-MS (method B): m/z: 566, R_t = 7.69 min.

EXAMPLE 74 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid

20



^1H NMR ($\text{DMSO}-d_6$): δ 8.80 (1H, s), 8.48 (1H, t), 8.05 (1H, s), 7.82 (1H, d), 7.77 (1H, d), 7.58 (1H, d), 7.32 (1H, s).

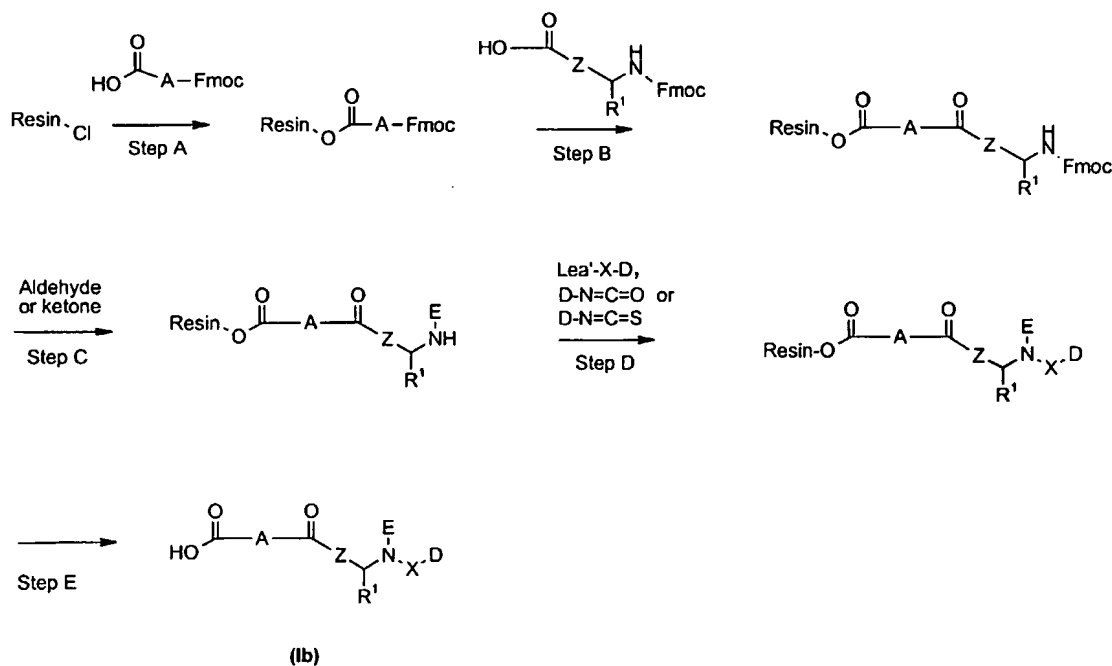
HPLC-MS (method B): m/z : 583, R_t = 8.03 min.

5

General procedure (D) for the solid phase synthesis of compounds of the general formula (Ib):

The compounds of the general formula (Ib) may also be prepared by the use of the following method:

10

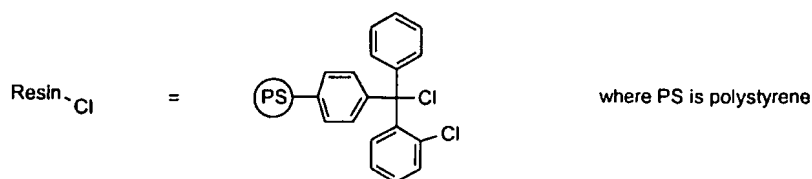


wherein

15 R^1 , A, Z, E and D are as defined for formula (I),

X is $-\text{S}(\text{O})_2-(\text{CH}_2)_r-$, $-\text{C}(\text{O})\text{NH}-$ or $-\text{C}(\text{S})\text{NH}-$, wherein r is as defined for formula (I),

Lea' represents a leaving group such as $-\text{OSu}$, $\text{Cl}-$, $\text{PhO}-$, or $4\text{-NO}_2\text{-PhO}-$, and

Step A:

- The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of an Fmoc amino acid in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotritylchloride.

Step B:

- The Fmoc protecting group is removed using a solution of 20% piperidine in DMF, which is added to the resin and vortexed for 0.5 hours. After draining the resin is washed with DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF.

- The acylation (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) is performed by adding an excess of Fmoc amino-benzoic acid in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of the these, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1H-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

Step C:

The Fmoc protecting group is removed eg using a solution of 20% piperidine in DMF. The reductive amination is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 167) and is performed by stirring resin bound amine with an excess of ketone or aldehyde at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of the above. As reducing agent sodium trisacetoxy borohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction optionally in combination with water.

Step D:

The reaction is generally known (Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, 62, 6090-6092) and is usually performed by shaking resin bound amine with an excess of isocyanate or an equivalent such as a carbamate Lea'-X-D in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, DMSO or a mixture of two or more of the above and when using Lea'-X-D in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate. The reaction is performed between 20°C and 120°C, preferably between 20°C and 40°C. Excess reagent is filtered off and the resin is washed several times with the solvent used during the reaction.

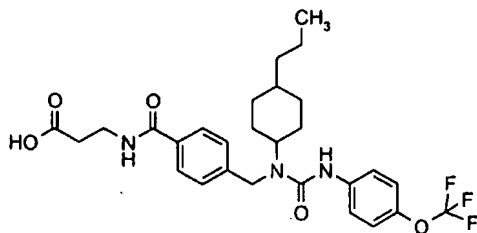
Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring the resin bound intermediate with a 5-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or more of the above. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with the solvent used during the reaction, optionally containing TFA. The product and washings are collected and the solvent is removed in vacuo.

A specific example illustrating the preparation of compounds of the general formula (Ib) according to the invention is provided below.

EXAMPLE 75 (general procedure (D))

3-{4-[1-(4-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



5

Step A: Resin bound Fmoc β -alanine

150 μ mol Fmoc β -alanine was dissolved in a mixture of 250 μ L dichloromethane, 250 μ L DMF and 100 μ L diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotrityl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane:methanol:diisopropyl-
 10 ethylamine 17:2:1 and 2 x 1 mL DMF.

Step B: Resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}-propionic acid

To the above resin bound Fmoc β -alanine was added 500 μ L of a 20% solution of piperidine in DMF. Upon shaking 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200 μ mol 4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoic acid (74.2 mg) dissolved in a mixture of 430 μ L DMF and 70 μ L diethylisopropylamine was added followed by 200 μ mol bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500 μ L DMF. The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with 3 x 1 mL DMF.

Step C: Resin bound 3-{4-[(4-propylcyclohexylamino)methyl]benzoylamino}propionic acid

The Fmoc protecting group was removed from the above resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}propionic acid using 500 μ L of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL), 2 x 1 mL 1,2-dichloroethane and 20 μ L acetic acid dissolved in 1 mL 1,2-dichloroethane.

30

The resulting resin bound 3-(4-aminomethylbenzoylamino)propionic acid was treated with 98 mg 4-propylcyclohexanone (700 μ mol) dissolved in 500 μ L 1,2-dichloroethane, 50 μ L acetic acid and a slurry of 148 mg NaBH(OAc)₃ (700 μ mol) in 1 mL 1,2-dichloroethane. Over night shaking at 25°C followed by filtration and washing with 2 x 1 mL dichloromethane, 2 x 1 mL CH₃OH:DMF 1:1 and 3 x 1 mL DMF afforded resin bound 3-{4-[(4-propylcyclohexylamino)-methyl]benzoylamino}propionic acid.

Step D: Resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

200 μ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500 μ L 1,2-dichloroethane was added to the above resin bound 3-{4-[(4-propylcyclohexylamino)methyl]benzoylamino}-propionic acid. Shaking the mixture for 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF, 3 x 1 mL dichloromethane afforded the resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid.

Step E: 3-{4-[1-(4-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

The above resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L CH₃CN and purified by preparative HPLC using a Supelcosil ABZ+ 25 cmx10 mm 5 μ column. The starting eluent composition was 5% CH₃CN in H₂O changing over 30 minutes to 90% CH₃CN in H₂O which was then kept constant for 5 minutes before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min. collecting one fraction per minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired products were combined and evaporated in vacuo to afford the title compound.

30

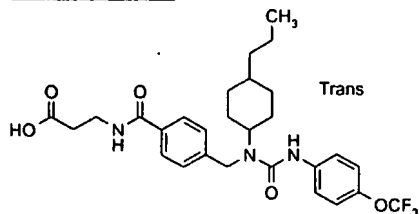
HPLC-MS (method B) (m/z = 550), (7.46, 7.58 min)

The HPLC purification allowed the separation of the *cis* and *trans* isomers of the title compound. The products were characterized by HPLC-MS and ¹H NMR.

35

EXAMPLE 76 (general procedure (D))

3-{4-[1-(4-*trans*-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



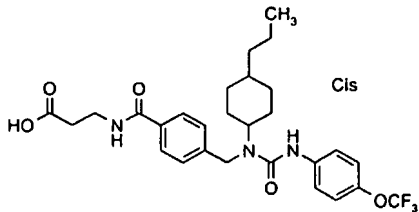
5

¹H NMR (400 MHz), (DMSO-*d*₆): δ 12.20 (s br, 1H); 8.55 (s, 1H); 8.50 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.10 (t, 1H); 3.40 (m, 2H); 2.45 (t, 2H); 0.70-1.80 ppm (m, 16H).

10 HPLC-MS (method B) (m/z = 550), (R_t = 7.46 min).

EXAMPLE 77 (general procedure (D))

3-{4-[1-(4-*cis*-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



15

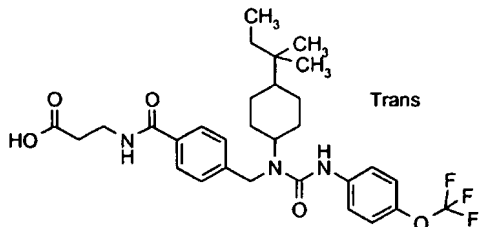
¹H NMR (400 MHz), (DMSO-*d*₆): δ 12.15 (s br, 1H); 8.55 (s, 1H); 8.50 (t, 1H); 7.80 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.25 (d, 2H); 4.65 (s, 2H); 4.10 (s br, 1H); 3.45 (m, 2H); 2.50 (2H); 1.15-1.65 ppm (m, 13H), 0.85 (t, 3H).

20

HPLC-MS (method B) (m/z = 550), (7.58 min).

EXAMPLE 78 (general procedure (D))

3-{4-[1-[4-*trans*-(1,1-Dimethylpropyl)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

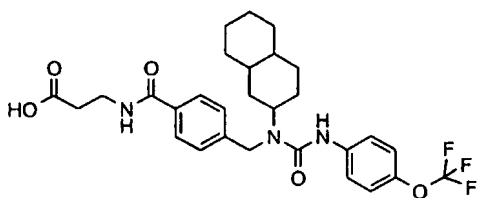


5

HPLC-MS (method B) (m/z = 578) (7.84 min, 7.94 min).

EXAMPLE 79 (general procedure (D))

3-{4-[1-(Decahydronaphthalen-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



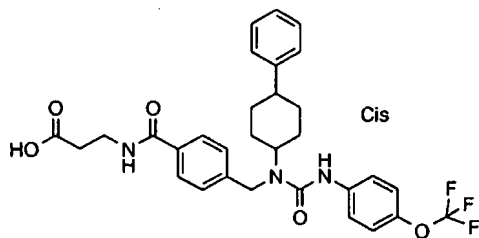
10

^1H NMR (400 MHz, DMSO- d_6): δ 8.50 (s, 1H); 8.47 (t, 1H); 7.76 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.22 (d, 2H); 4.60 (s, 2H); 4.30 (t, 1H); 3.45 (m, 2H); 2.50 (t, 2H); 1.85-0.70 (m).

15 HPLC-MS (method B) (m/z = 562) (7.48 min, 7.49 min).

EXAMPLE 80 (general procedure (D))

3-{4-[1-(4-*cis*-Phenylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

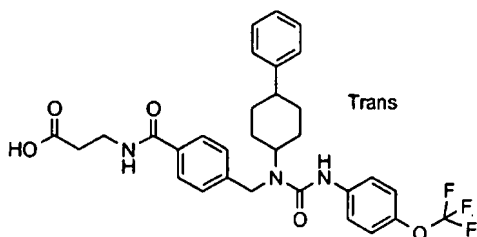


20

HPLC-MS (method B) (m/z = 584), (7.22 min, 7.33 min).

EXAMPLE 81 (general procedure (D))

3-{4-[1-(4-*trans*-Phenylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

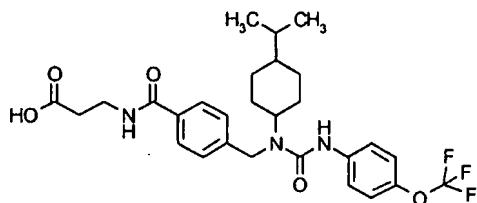


5

HPLC-MS (method B) (m/z = 584), (7.22 min, 7.33 min).

EXAMPLE 82 (general procedure (D))

10 3-{4-[1-(4-Isopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

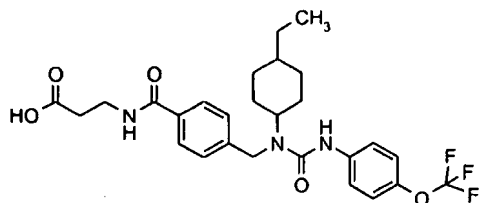


15 ^1H NMR (200 MHz), (DMSO- d_6): δ 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.05-4.15 (m br, 1H); 3.45 (m, 2H); 2.50 (t, 2H); 0.90-1.8 (m, 10H); 0.85 (d, 6H).

HPLC-MS (method B) (m/z = 550), (R_t = 7.38 min, 7.50 min)

EXAMPLE 83 (general procedure (D))

3-{4-[1-(4-Ethylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



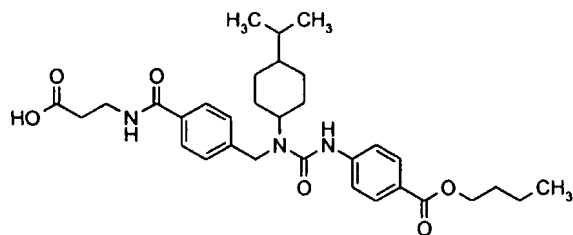
5

^1H NMR (300 MHz), (DMSO- d_6): δ 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.25 (d, 2H); 4.60 (s, 2H); 4.05-4.15 (m br, 1H); 3.45 (m, 2H); 2.50 (t, 2H); 0.75-1.8 (m, 14H).

10 HPLC-MS (method B) (m/z = 536), (R_t = 7.59 min).

EXAMPLE 84 (general procedure (D))

4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(4-isopropylcyclohexyl)ureido]benzoic acid butyl ester

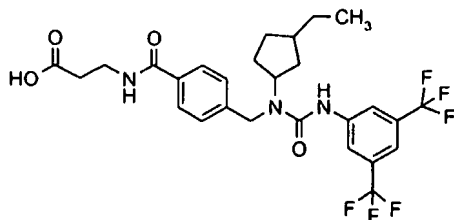


15

^1H NMR (DMSO- d_6): δ 8.70 (s, 1H); 8.45 (t, 1H); 7.83 (d, 2H); 7.78 (d, 2H); 7.60 (d, 2H); 7.34 (d, 2H); 4.67 (s, 2H); 4.24 (t, 2H); 4.14 (m, 1H); 0.96 (t, 3H); 0.85 (d, 6H).

EXAMPLE 85 (general procedure (D))

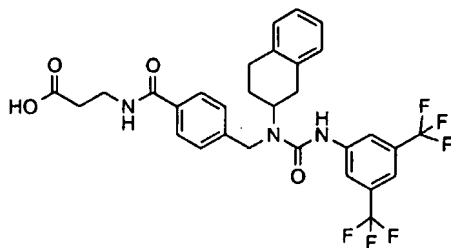
3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(3-ethylcyclopentyl)ureidomethyl]benzoylamino}-propionic acid



- 5 ^1H NMR (DMSO- d_6): δ 9.04 (s, 1H); 8.48 (t, 1H); 8.28 (s, 2H); 7.71 (d, 2H); 7.62 (s, 1H); 7.84 (d, 2H); 4.65 (s, 2H).

EXAMPLE 86 (general procedure (D))

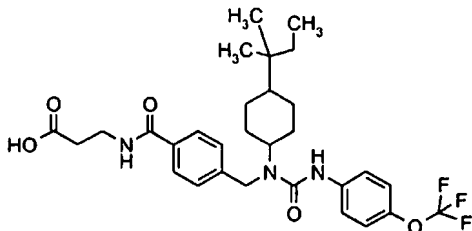
10 3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(1,2,3,4-tetrahydronaphthalen-2-yl)ureidomethyl]-benzoylamino}propionic acid



- 15 ^1H NMR (DMSO- d_6): δ 9.20 (s, 1H); 8.50 (t, 1H); 8.82 (s, 2H); 7.81 (d, 2H); 7.62 (s, 1H); 7.42 (d, 2H); 7.10 (m, 4H); 4.75 (dd, 2H); 4.52 (m, 1H).

EXAMPLE 87 (general procedure (D))

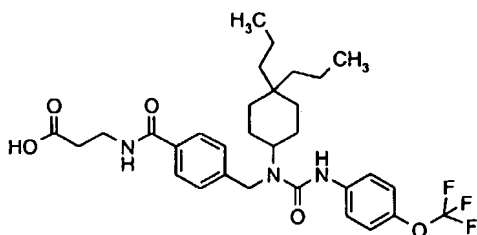
3-{4-[1-[4-(1,1-Dimethylpropyl)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid



^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.05 (s br) 8.60 (s); 8.55 (s); 8.45 (t); 7.80 (d); 7.55 (d); 7.30 (d); 7.20 (d); 4.72 (s); 4.60 (s); 4.25 (t); 4.05 (t); 3.45 (q); 2.50 (t); 1.90-1.00 (m) 0.77 (s); 0.73 (s).

5 EXAMPLE 88 (general procedure (D))

3-{4-[1-(4,4-Dipropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



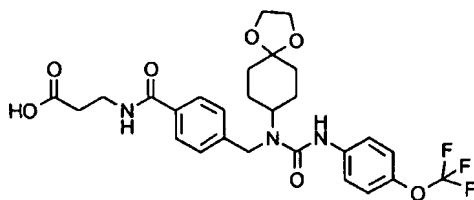
10 ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.52 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.62 (s, 2H); 4.05 (t, 1H); 3.45 (q, 2H); 2.45 (t, 2H); 1.70-0.70 (m, 22H).

HPLC-MS (method B): m/z = 592, R_t = 8.60 min.

15 The compounds of the invention can also be prepared by conventional solution phase synthesis methods as described below:

EXAMPLE 89

20 3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



25 Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride was prepared from β -alanine ethyl ester hydrochloride and 4-(*tert*-butoxycarbonylaminomethyl)benzoic acid by methods known to those skilled in the art.

3-{4-[(1,4-Dioxaspiro[4.5]dec-8-ylamino)methyl]benzoylamino}propionic acid ethyl ester

1.2 g Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride (4.18 mmol) was mixed with 20 mL 1,2-dichloroethane and 6 mL saturated K_2CO_3 by vigorous stirring. The phases were separated and the aqueous phase was extracted with another 20 mL 1,2-dichloroethane. 240 μ L HOAc was added to the combined 1,2-dichloroethane phase followed by 0.691 g 1,4-dioxaspiro[4.5]decan-8-one (4.42 mmol). 1.272 g $NaBH(OAc)_3$ (6 mmol) was added and the reaction was stirred for 16 hours at 25°C. The reaction volume was reduced on a rotary evaporator to about 20 mL and then poured into a mixture of 60 mL H_2O and 10 mL sat. K_2CO_3 . The phases were separated and the aqueous phase was extracted twice with 40 mL 1,2-dichloroethane. The combined 1,2-dichloroethane fractions were dried over $MgSO_4$ and evaporated to afford the title compound. The crude product was used in the next step without further purification.

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester

0.312 g 4-Trifluoromethoxyphenylisocyanate dissolved in 1 mL acetonitrile was added to 0.5 g of the above 3-{4-[(1,4-dioxaspiro[4.5]dec-8-ylamino)methyl]benzoylamino}propionic acid ethyl ester dissolved in 5 mL acetonitrile and was allowed to react at 25°C. The product precipitated after 1 hour and was collected by filtration.

1H NMR (400 MHz), ($DMSO-d_6$): δ 8.55 (s, 1H); 8.50 (t, 1H); 7.75 (d, 2H); 7.50 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.20 (s br, 1H); 4.05 (q, 2H); 3.75 (s, 4H); 3.30 (m, 2H); 2.60 (t, 2H); 1.60-1.70 (m, 8H); 1.15 (t, 3H)

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

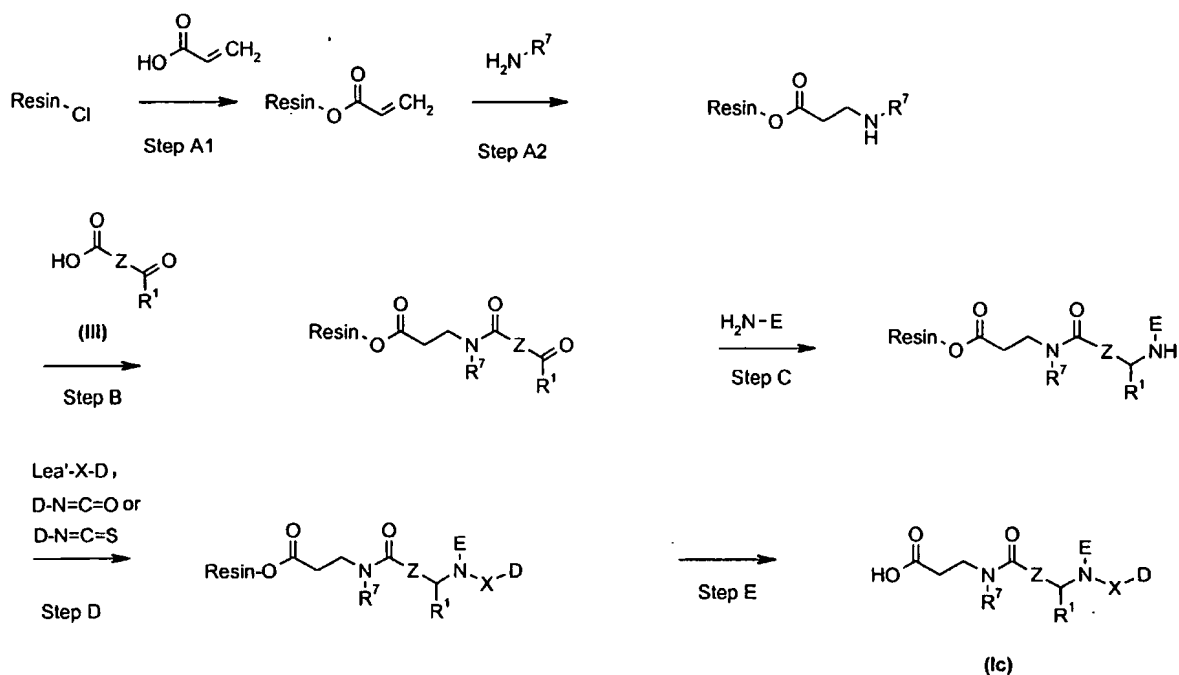
180 mg LiOH dissolved in 2.2 mL H_2O was added to the entire yield of the above 3-{4-[1-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester dissolved in 22 mL abs. EtOH. After 1 hour at 25°C the solvent was evaporated and 10 mL H_2O followed by 500 mg citric acid dissolved in 20 mL H_2O was added to the residue affording a pH of 4-5. The resulting product was a mixture of the acid and its lithium salt.

^1H NMR (400 MHz), ($\text{DMSO}-d_6$ +TFA): δ 8.60 (s, 1H); 8.50 (t, 1H); 7.80 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.20 (s br, 1H); 3.80 (s, 4H); 3.45 (m, 2H); 2.50 (t, 2H); 1.55-1.75 (m, 8H).

- 5 HPLC-MS (method B) ($m/z = 566 \text{ M}+1$), ($R_t = 6.10 \text{ min}$).

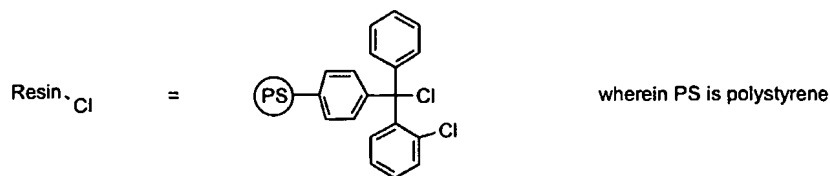
General procedure (E) for the solid phase synthesis of compounds of the general formula (Ic):

- 10 Compounds of the general formula (Ic) according to the invention can be synthesized on solid support using a procedure comprising attachment of acrylic acid to a polystyrene 2-chlorotriptylchloride resin followed by a Michael addition of $\text{R}^7\text{-NH}_2$. Acylation followed by reductive amination and urea formation as described above affords the desired compounds:



15

wherein



Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy,

R¹, E and D are as defined for formula (I),

5

R⁷ is C₁₋₆-alkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl, and

X is -S(O)₂-(CH₂)_r-, -C(O)NH- or -C(S)NH-, wherein r is as defined for formula (I),

10 Step A1:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of acrylic acid in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotriethylchloride.

20

Step A2:

The reaction is known (Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. J. *Org. Chem.* **1998**, 63, 703-718) and is performed by shaking the resin bound acrylic acid with an excess of a primary amine in a solvent such as DMSO, DMF, NMP, THF, methanol, ethanol, dichloromethane, 1,2-dichloroethane or a mixture of two or more of these. The reaction is carried out between 20°C and 120°C, preferably at 25°C. Excess amine is filtered off and the resin is washed several times with the solvent used during the reaction.

25

Step B:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) and is performed by adding an excess of acid (III) in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of the above, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1H-

30

35

9-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-
5 1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazol. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess of reagents is filtered off and the resin is washed several times with the solvent used in the reaction.

Step C:

10 The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring the resin bound aldehyde or ketone obtained in step B with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture
15 of two or more of these. A reducing agent such as sodium cyanoborohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess of reagents is filtered off and the resin is washed several times with the solvent used in the reaction optionally in combination with water.

20 Step D:

The reaction is generally known (Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, 62, 6090-6092) and is usually performed by shaking resin bound amine obtained in step C with an excess of an isocyanate or isothiocyanate or alternatively Lea'-X-D in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, DMSO or a mixture of two or more of the
25 above and when using Lea'-X-D in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate. The reaction is performed between 20°C and 120°C, preferably between 20°C and 40°C. Excess of reagent is filtered off and the resin is washed several times with the solvent used in the reaction.

30

Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring the resin bound intermediate obtained in step D with a 5-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, di-
35 chloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or

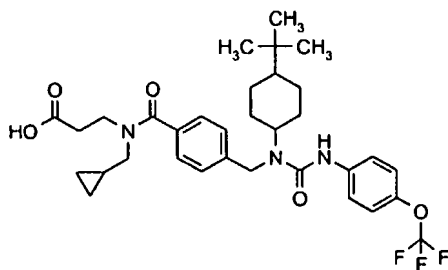
more of these. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with the solvent used in the reaction, optionally containing TFA. The product and washings are collected. The solvent is removed in vacuo.

5

The following examples were prepared according to general procedure (E).

EXAMPLE 90 (general procedure (E))

3-((4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl)-
10 cyclopropylmethyl)aminopropionic acid



Step A1: Resin bound acrylic acid

15 150 µmol acrylic acid was dissolved in a mixture of 500 µL dichloromethane and 100 µL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol: diisopropylethylamine 17:2:1 and 2 x 1 mL DMSO.

20 Step A2: Resin bound *N*-(cyclopropylmethyl)-3-aminopropionic acid

The above resin bound acrylic acid (50 mg) was treated with 300 µmol cyclopropylmethyl amine (21.3 mg) in 300 µL DMSO for 72 hours at 25°C. The excess reagent was filtered off and the resin was washed with 3 x 1 mL DMSO and 3 x 1 mL DMF.

25 Step B: Resin bound 3-[cyclopropylmethyl-(4-formylbenzoyl)amino]propionic acid

To the above resin bound *N*-(cyclopropylmethyl) 3-aminopropionic acid (50 mg) was added 200 µmol 4-formylbenzoic acid (30 mg) dissolved in a mixture of 430 µL DMF and 70 µL diisopropylethylamine followed by 200 µmol bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500 µL DMF. The mixture was shaken at 25°C for 4

hours followed by filtration and washing of the resin with 3 x 1 mL DMF and 1 mL trimethyl-orthoformate.

Step C: Resin bound 3-({4-[1-(4-*tert*-butylcyclohexylamino)methyl]benzoyl}cyclopropylmethyl-
amino)propionic acid

The above resin bound 3-[cyclopropylmethyl-(4-formylbenzoyl)amino]propionic acid (50 mg) was treated with 1 mL 0.5 M (0.5 mmol, 77.5 mg) 4-*tert*-butylcyclohexylamine solution in DMF:trimethylorthoformate 1:1, 100 μ L glacial acetic acid and sodium cyanoborohydride (750 μ mol, 48 mg) suspended in 0.5 mL DMF:trimethylorthoformate 1:1. Overnight shaking at 25°C followed by filtration and washing with 2 x 1 mL 20% H₂O in DMF, 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

Step D: Resin bound 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureido-methyl]benzoyl}cyclopropylmethyl)aminopropionic acid

200 μ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500 μ L dichloromethane was added to the above resin bound 3-({4-[1-(4-*tert*-butylcyclohexylamino)methyl]benzoyl}-cyclopropylmethyl)aminopropionic acid (50 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

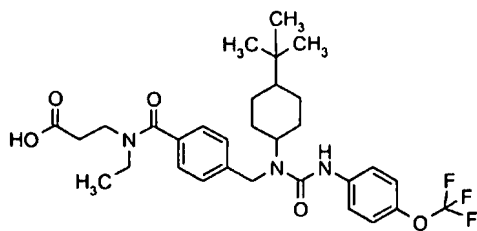
Step E: 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}-cyclopropylmethyl)aminopropionic acid

The above resin bound 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureido-methyl]benzoyl}cyclopropylmethyl)aminopropionic acid (50 mg) was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 μ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction per minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

The product was characterized by HPLC-MS (Method B): R_t = 7.91 min, m/z = 618 (M+1).

EXAMPLE 91 (general procedure (E))

3-((4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl)ethyl-amino)propionic acid

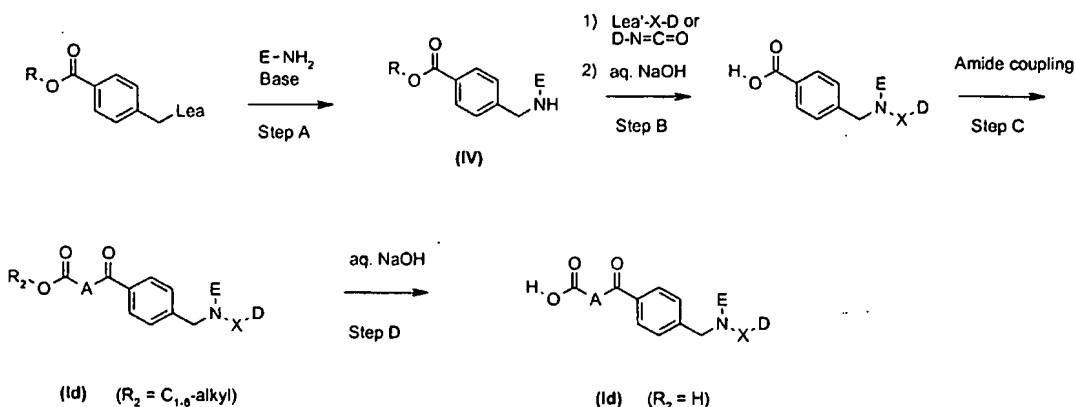


5

The product was characterized by HPLC-MS (Method B): $R_t = 7.94$ min, $m/z = 592$ ($M+1$).

The compounds of the invention can also be prepared by conventional solution phase synthesis methods as the following general method describes.

10

General procedure (F) for the solution phase synthesis of compounds of general formula (Id):

15

wherein R is C_{1-6} -alkyl,

A, X, D, and E are as defined in general formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl, or tosyl, and

20

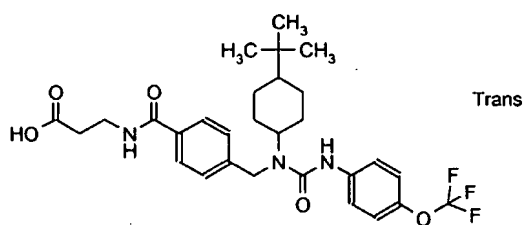
Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these may be performed eg by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

- 5 The procedure is illustrated in example 92.

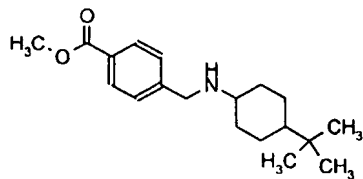
EXAMPLE 92 (general procedure (F))

3-{4-[1-(4-*trans-tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



10

Step A: 4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester



- 15 4-(Bromomethyl)benzoic acid methyl ester (5.0 g, 22 mmol) and 4-*tert*-butylcyclohexylamine (*cis/trans* mixture) (3.4 g, 22 mmol) were dissolved in DMF where after potassium carbonate (6.1 g, 44 mmol) was added. The reaction mixture was stirred at 100°C for 7 hours and for 16 hours at 20°C. Water (100 mL) and ethyl acetate (200 mL) were added to the reaction mixture. The organic phase was isolated and washed with water (2 x 100 mL) and a saturated solution of sodium chloride (2 x 100 mL). The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to give a *cis/trans* mixture of 4-[(4-*tert*-butylcyclohexylamino)methyl]-benzoic acid methyl ester as a crude product. The two isomers were separated on silica (110 g) using a mixture of ethyl acetate and dichloromethane (7:3) as eluent.
- 20

trans isomer:

Micro analysis: Calculated for $C_{19}H_{29}NO_2$:

C: 75.21, H: 9.63, N: 4.62%. Found:

C: 75.02, H: 9.80, N: 4.64%.

5

HPLC-MS (Method B): $R_t = 5.23$ min, $m/z = 304$ ($M + 1$).

1H NMR (DMSO- d_6), 400 MHz: δ 7.90 (d, 2H), 7.48 (d, 2H), 3.82 (s, 3H), 3.78 (s, 2H), 2.30-2.20 (m, 1H), 2.05-1.90 (m, 3H), 1.73-1.65 (m, 2H), 1.10-0.90 (m, 4H), 0.80 (s, 9H).

10

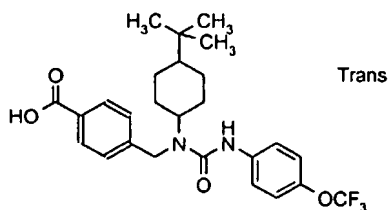
cis isomer:

HPLC-MS (Method B): $R_t = 4.83$ min, $m/z = 304$ ($M + 1$).

1H NMR (DMSO- d_6), 400 MHz: δ 7.92 (d, 2H), 7.58 (d, 2H), 3.90 (dd, 1H), 3.85 (s, 3H), 3.80 (dd, 1H), 2.50-2.35 (m, 1H), 2.00-1.85 (m, 2H), 1.80-1.70 (m, 2H), 1.70-1.45 (m, 2H), 1.00-0.80 (m, 1H), 0.80 (s, 9H).

15

Step B: 4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid



20

4-[(*trans*-4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (2.6 g, 8.6 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (1.7 g, 8.6 mmol) were dissolved in acetonitrile (40 mL) and stirred at 20°C for 16 hours. The reaction mixture was concentrated in vacuo and the crude product purified on silica (100 g) using heptane and ethyl acetate (3:1) as eluent to give 4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester. The product was suspended in ethanol (80 mL) and sodium hydroxide (4N, 17 mL) was added. The reaction mixture was stirred at 50°C for 3 hours and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (100 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (3 x 75 mL) and the combined organic phases were dried ($MgSO_4$) and concen-

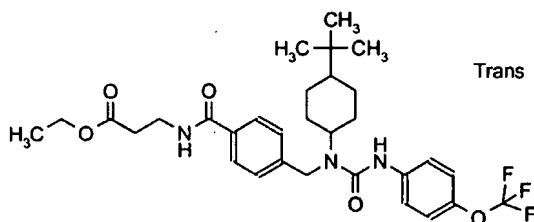
30

trated in vacuo to give 4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoic acid.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.80 (s, 1H), 8.55 (s, 1H), 7.90 (d, 2H), 7.55 (d, 2H), 7.35 (d, 2H), 7.21 (d, 2H), 4.62 (s, 2H), 4.10-4.00 (m, 1H), 2.00 (s, 2H), 1.80-1.60 (m, 4H), 1.48-1.38 (m, 2H), 1.20-1.00 (m, 2H), 1.00-0.88 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 8.37 min, m/z = 493 (M + 1).

10 Step C: 3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid ethyl ester



4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid (2.0 g, 4.1 mmol), 1-hydroxybenzotriazole (0.6 g, 4.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.8 g, 4.3 mmol) were dissolved in DMF (40 mL). A solution of diisopropylethylamine (0.5 g, 4.1 mmol) and 3-aminopropionic acid ethyl ester, hydrochloride (0.4 g, 4.3 mmol) in DMF (10 mL) was added and the reaction mixture was stirred for 16 hours at 20°C. Ethyl acetate (150 mL) and water (100 mL) were added and the organic phase isolated. The aqueous phase was extracted with ethyl acetate (50 mL) and the organic phases combined, dried (MgSO₄) and concentrated in vacuo. The crude product was purified on silica (80 g) using heptane and ethyl acetate (1:1) as eluent to give 3-{4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester.

25

M.p. = 108-111°C.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 8.55 (s, 1H), 8.50 (t, 1H), 7.75 (d, 2H), 7.55 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.60 (s, 2H), 4.10-4.00 (m, 1H), 3.60 (s, 3H), 3.45 (dd, 2H), 2.55 (t, 2H), 1.80-1.60 (m, 4H), 1.50-0.80 (m, 5H), 0.80 (s, 9H).

30

HPLC-MS (Method B): $R_t = 8.43$ min, $m/z = 578$ ($M + 1$).

Step D:

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-
5 amino}propionic acid ethyl ester (1.4 g, 2.4 mmol) was suspended in ethanol (50 mL) and sodium hydroxide (4 N, 6 mL) added. The reaction mixture was stirred for 2 hours at 50°C and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (100 mL) and adjusted to pH 2 with hydrochloric acid (4N), and the title compound was isolated by filtration.

10

M.p. = 152-154°C.

^1H NMR (DMSO- d_6), 400 MHz: δ 12.20 (s, 1H), 8.55 (s, 1H), 7.95 (t, 1H), 7.75 (d, 2H), 7.55 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.60 (s, 2H), 4.10-4.00 (m, 1H), 3.45 (dd, 2H), 2.50 (2H),
15 1.80-1.60 (m, 4H), 1.45-1.35 (m, 2H), 1.15-1.05 (m, 2H), 0.95-0.85 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): $R_t = 7.88$ min, $m/z = 564$ ($M + 1$).

Micro analysis: Calculated for $\text{C}_{29}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_5$, $0.75\text{H}_2\text{O}$:

20 C: 60.35, H: 6.55, N: 7.28%. Found:

C: 60.47, H: 6.32, N: 7.32%.

Alternative method for the preparation of the compound (general procedure (K)):

General procedure (K) is described in the following:

Step 6, using pure isocyanate prepared from (substituted) anilines and diphosgene as described under the general procedure (K):

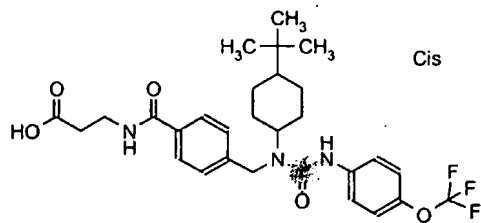
- 5 Methyl *trans*-4-[(4-*tert*-butylcyclohexyl)aminomethyl]benzoylaminopropanoate, hydrochloride (10.0 g 24 mmol, prepared by using anhydrous hydrogen chloride in ethyl acetate in general procedure (K), step 5) was suspended in acetonitrile (300 mL) and diisopropylethylamine (4.14 mL, 24 mmol) was added. To this suspension 4-trifluoromethoxyphenylisocyanate
- 10 (3.75 mL, 24 mmol) was added. Stirring at room temperature was continued for 4 hours and then the mixture was left at 5°C for 16 hours. Filtration and washing with cold acetonitrile afforded 11.9 g (85%) of 3-{4-[1-(4-*trans*-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoylamino}propionic acid methyl ester.

15 Step 7:

Hydrolysis of this ester using the method described in example 46, step D afforded the title compound (11 g, 94%).

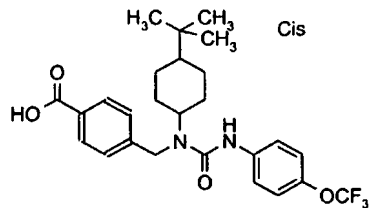
EXAMPLE 93

- 20 3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxy-phenyl)ureidomethyl]-benzoylamino}propionic acid



Step A: 4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid

- 25 acid



4-[(*cis*-4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (0.36 g, 1.2 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (0.24 g, 1.2 mmol) were dissolved in acetonitrile (10 mL) and stirred at 20°C for 16 hours. The reaction mixture was concentrated in vacuo and the crude product purified on silica (25 g) using heptane and ethyl acetate (9:1) as eluent to give 4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester. The product was suspended in ethanol (10 mL) and sodium hydroxide (4N, 1.1 mL) was added. The reaction mixture was stirred at 50°C for 3 hours and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (50 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (75 mL) and the organic phase was dried (MgSO₄) and concentrated in vacuo to give 4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid.

Micro analysis: Calculated for C₂₆H₃₁F₃N₂O₄:

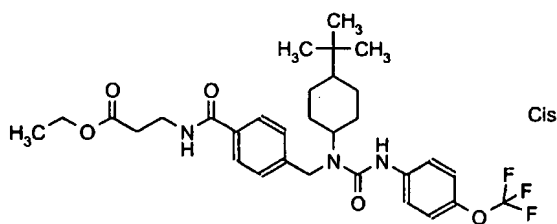
C: 63.40, H: 6.34, N: 5.69%. Found:

C: 63.29, H: 6.33, N: 5.65%.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.80 (s, 1H), 8.61 (s, 1H), 7.90 (d, 2H), 7.55 (d, 2H), 7.35 (d, 2H), 7.22 (d, 2H), 4.72 (s, 2H), 4.32-4.22 (m, 1H), 1.85-1.70 (m, 2H), 1.65-1.45 (m, 4H), 1.40-1.10 (m, 3H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 7.85 min, m/z = 493 (M + 1).

Step B: 3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid ethyl ester



4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid (0.3 g, 0.6 mmol), 1-hydroxybenzotriazole (0.1 g, 0.7 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.13 g, 0.7 mmol) were dissolved in DMF (10 mL). Diisopropylethylamine (0.1 g, 0.7 mmol) and 3-aminopropionic acid ethyl ester, hydrochloride (0.07 g, 0.7

mmol) in DMF was added and the reaction mixture was stirred for 16 hours at 20°C. Ethyl acetate (80 mL) and water (50 mL) were added and the organic phase isolated. The aqueous phase was extracted with ethyl acetate (50 mL) and the organic phases combined, dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from heptane and ethyl acetate (4:1) to give 3-{4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester.

M.p. = 87-90°C.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 8.60 (s, 1H), 8.48 (t, 1H), 7.75 (d, 2H), 7.52 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 4.70 (s, 2H), 4.30-4.20 (m, 1H), 3.60 (s, 3H), 3.48 (dd, 2H), 2.55 (t, 2H), 1.82-1.70 (m, 2H), 1.60-1.45 (m, 4H), 1.40-1.10 (m, 3H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 7.80 min, m/z = 578 (M + 1).

Micro analysis: Calculated for C₃₀H₃₈F₃N₃O₅:

C: 62.38, H: 6.63, N: 7.27%. Found:

C: 62.49, H: 6.75, N: 7.20%.

Step C:

3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid ethyl ester (0.2 g, 0.3 mmol) was suspended in ethanol (8 mL) and sodium hydroxide (4N, 0.6 mL) added. The reaction mixture was stirred for 16 hours at 20°C and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (50 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (80 mL) and the organic phase was dried (MgSO₄) and concentrated in vacuo to give the title compound.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.20 (s, 1H), 8.60 (s, 1H), 8.45 (t, 1H), 7.77 (d, 2H), 7.53 (d, 2H), 7.28 (d, 2H), 7.20 (d, 2H), 4.70 (s, 2H), 4.30-4.20 (m, 1H), 3.45 (dd, 2H), 2.50 (2H), 1.82-1.70 (m, 2H), 1.60-1.45 (m, 4H), 1.40-1.30 (m, 2H), 1.20-1.10 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 7.32 min, m/z = 564 (M + 1).

Micro analysis: Calculated for C₂₉H₃₆F₃N₃O₅, 0.25H₂O:

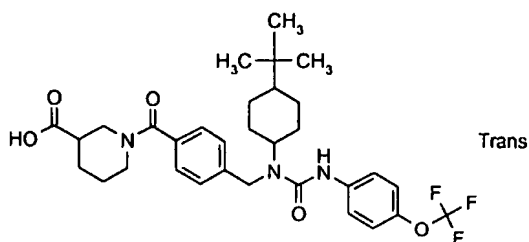
C: 61.53, H: 6.54, N: 7.18%. Found:

C: 61.36, H: 6.80, N: 7.09%.

5 The following compounds were prepared using the general procedure (F) as described above.

EXAMPLE 94 (general procedure (F))

1-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}-
piperidine-3-carboxylic acid



The compound was prepared using nipecotic acid methyl ester, hydrochloride instead of 3-aminopropionic acid methyl ester, hydrochloride in step C.

15 HPLC-MS (Method B): $R_t = 8.17$ min, $m/z = 604$ ($M + 1$).

Micro analysis: Calculated for $C_{32}H_{40}F_3N_3O_5$:

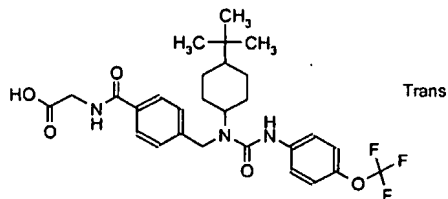
C: 63.67, H: 6.68, N: 6.96%. Found:

C: 63.66, H: 6.75, N: 6.94%.

20

EXAMPLE 95 (general procedure (F))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-
benzoylamino}acetic acid



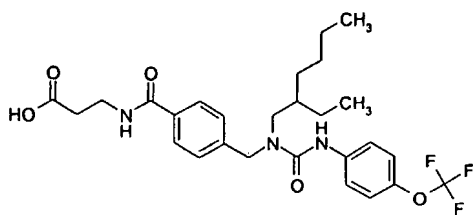
¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.55 (s, 1H), 8.76 (t, 1H), 8.52 (s, 1H), 7.81 (d, 2H), 7.55 (d, 2H), 7.33 (d, 2H), 7.22 (d, 2H), 4.61 (s, 2H), 4.10-4.00 (m, 1H), 3.80 (d, 2H), 1.75-1.60 (m, 4H), 1.45-1.30 (m, 2H), 1.20-1.00 (m, 2H), 1.00-0.80 (m, 1H), 0.80 (s, 9H).

5

HPLC-MS (Method B): *R*_t = 7.88 min, *m/z* = 550 (*M* + 1).

EXAMPLE 96 (general procedure (F))

3-{4-[1-(2-Ethylhexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



10

The compound was prepared using 2-ethylhexylamine instead of 4-*tert*-butylcyclohexylamine in step A.

15 ¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.20 (s, 1H), 8.63 (s, 1H), 8.49 (t, 1H), 7.82 (d, 2H), 7.54 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.65 (s, 2H), 3.45 (dd, 2H), 3.25 (m, 2H), 2.50 (2H), 1.70-1.60 (m, 1H), 1.40-1.10 (m, 8H), 0.90-0.70 (m, 6H).

HPLC-MS (Method B): *R*_t = 7.17 and 7.25 min, *m/z* = 538 (*M* + 1).

20

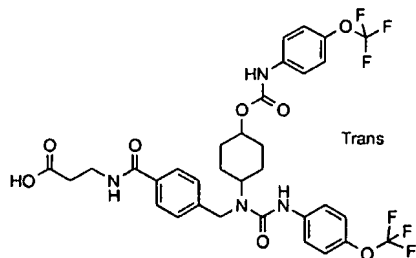
Micro analysis: Calculated for C₂₇H₃₄F₃ N₃O₅:

C: 60.33, H: 6.37, N: 7.82%. Found:

C: 60.51, H: 6.60, N: 7.48%.

EXAMPLE 97

3-{4-[1-(*trans*-4-(4-Trifluoromethoxyphenyl)carbamoyloxy)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

This compound was prepared on solid support using the same methodology as described in general procedure (F) using *trans* 4-hydroxycyclohexylamine instead of 4-*tert*-butylcyclohexylamine.

10 HPLC-MS (Method B): $R_t = 7.68$ min, $m/z = 727$ ($M + 1$).

Micro analysis: Calculated for $C_{33}H_{32}F_3N_4O_8$:

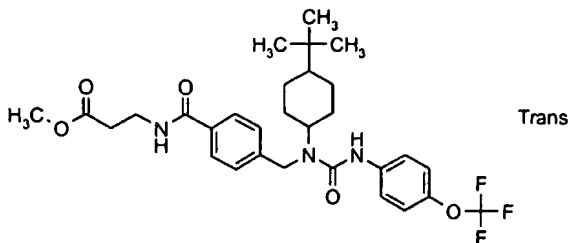
C: 54.55, H: 4.44, N: 7.71%. Found:

C: 54.17, H: 4.53, N: 7.44%.

15

EXAMPLE 98 (general procedure (F))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester



20

The compound was prepared according to procedure (F) but omitting step D.

Micro analysis: Calculated for $C_{29}H_{38}F_3N_3O_5 \cdot 0.1H_2O$:

C, 61.87%; H, 6.44%; N, 7.46%. Found:

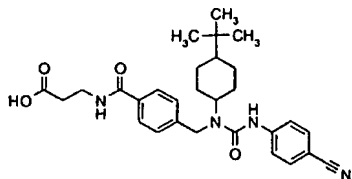
25 C, 61.60%; H, 6.45%; N, 7.43%.

HPLC-MS (Method B): m/z: 564.

EXAMPLE 99 (general procedure (F))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-cyanophenyl)ureidomethyl]benzoylamino}propionic acid

5



¹H NMR (DMSO-*d*₆): δ 12.2 (1H, broad), 8.82 (1H, s), 8.48 (1H, t), 7.78 (2H, d), 7.68 (4H, s), 7.32 (2H, d), 4.62 (2H, s), 4.05 (1H, m), 3.42 (2H, dd), 1.80-85 (9H, m), 0.80 (9H, s)

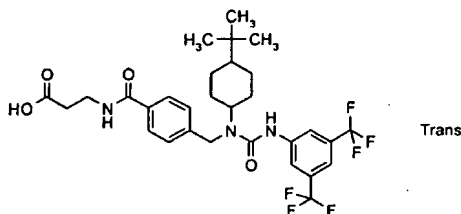
10

HPLC-MS (method B): m/z: 505, *R*_t = 7.28 min.

EXAMPLE 100 (general procedure (F))

3-{4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]benzoyl-
amino}propionic acid

15



The starting material, 4-[(*trans*-4-*tert*-butylcyclohexylamino)methyl]benzoic acid methyl ester, was prepared as described in step A of the general procedure (F).

20

¹H NMR (DMSO-*d*₆): δ 12.2 (s, 1H), 9.05(s, 1H), 8.45 (t, 1H), 8.25(s, 2H), 7.76(d, 2H), 7.61(s, 1H), 7.32(d, 2H), 4.63(s, 2H), 4.05(m, 1H), 3.45(m, 2H), 1.80-0.75 (m, 9H), 0.82 (s, 9H)

HPLC-MS (method B): m/z: 616, *R*_t = 8.3 min.

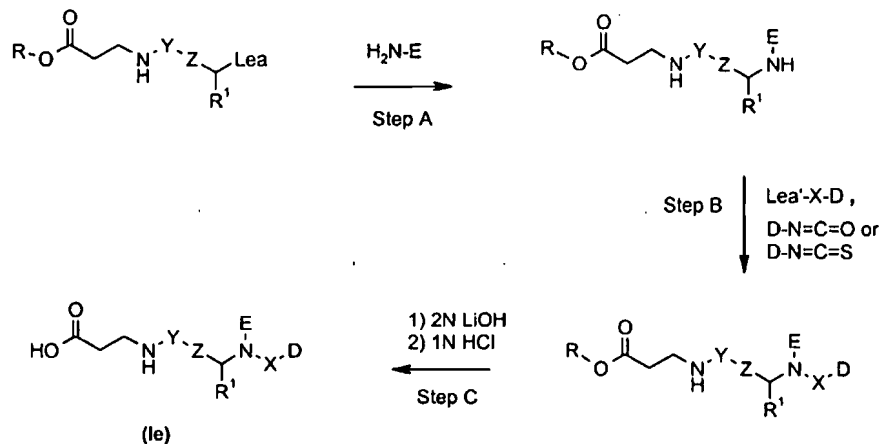
25

MA: calculated for C₃₀H₃₅F₆N₃O₄:

58.53% C; 5.73% H; 6.83% N; Found

58.25% C; 5.75% H; 7.02% N.

General procedure (G) for the solution phase synthesis of compounds of the general formula (Ie):



5

wherein

R^1 , E, Z and D are as defined for formula (I),

10 X is $-S(O)_2-(CH_2)_r-$, $-C(O)NH-$ or $-C(S)NH-$, wherein r is as defined for formula (I),

Y is $-C(O)-$ or $-S(O)_2-$,

R is C₁₋₆-alkyl,

15

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl, and

Lea' is a leaving group such as -OSu, chloro, phenoxy, 4-nitrophenoxy.

20 Step A:

The appropriate alkylhalide (0.02 mmol) in DMF was dispensed into the wells of a deepwell plate containing solid potassium carbonate (3 equivalents) and the appropriate amine, NH_2-E , (0.02 mmol). The reactions were agitated at room temperature for four hours and at 50°C for 12 hours. The solids were filtered off and the desired amines were used without further

25 purification in the next step.

Step B:

To the amines in DMF was added the desired isocyanate or isothiocyanate or alternatively Lea'-X-D (0.02 mmol) in DMF. When using Lea'-X-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was also added. The reactions are shaken for 30 minutes to give the desired ureas or thioureas.

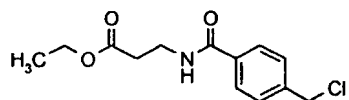
Step C:

To the crude products obtained in step B was added aqueous 2 N LiOH (10 equivalents). The samples were shaken overnight and filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

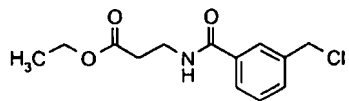
General preparation of halomethylarylcarboxamides as starting materials:

The halomethylarylcarboxamides were prepared from the coupling of the corresponding halomethylarylcarboxylic acid and the methyl or ethyl-3-aminopropionate hydrochloride according to the procedure described below.

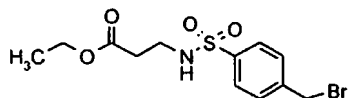
To a solution of the arylcarboxylic acid in a suitable solvent such as CH₂Cl₂, DMF or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before ethyl or methyl-3-aminopropionate hydrochloride (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1N HCl. The organic layer was separated and washed with H₂O (2 x), aqueous NaHCO₃ (3 x), brine (2 x), dried over MgSO₄ and concentrated to give the desired product.

25 Ethyl 3-[[4-(chloromethyl)benzoyl]amino]propionate:

¹H NMR (DMSO-*d*₆): δ 1.2 (t, 3H), 2.6 (t, 2H), 3.5 (qt, 2H), 4.1 (qt, 2H), 4.8 (s, 2H), 7.6 (d, 2H), 7.8 (d, 2H), 8.6 (t, 1H).

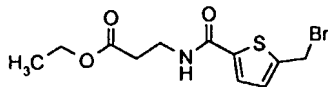
Ethyl 3-([3-(chloromethyl)benzoyl]amino)propionate:

¹H NMR (DMSO-*d*₆): δ 2.61 (t, 2H), 3.50 (qt, 2H), 3.61 (s, 3H), 4.81 (s, 2H), 7.47 (t, 1H), 7.59 (d, 1H), 7.79 (d, 1H), 7.90 (s, 1H), 8.62 (brd t, 1H).

Ethyl 3-([4-(bromomethyl)phenyl]sulfonyl)amino)propionate:

To a solution of the 4-bromomethylphenylsulfonylchloride (10 g, 37 mmol) in CH₂Cl₂ (200 mL) at 0°C was added diisopropylethylamine (16 mL, 93 mmol) followed by ethyl-3-aminopropionate hydrochloride (5.1 g, 37 mmol). The reaction was stirred for 10 minutes at 0°C and the solvent was evaporated at room temperature under reduced pressure. The residue was dissolved in ethyl acetate and washed with 1N HCl (3x), H₂O, aqueous NaHCO₃ (3x), brine (3x) and dried over MgSO₄. The solvent was concentrated to give a syrup. Addition of ethyl ether induced crystallization of the product as a white solid (10 g, 30 mmol, 81%).

¹H NMR (CDCl₃): δ 1.24 (t, 3H), 2.55 (t, 2H), 3.22 (qt, 2H), 4.13 (qt, 2H), 4.50 (s, 2H), 5.28 (t, 1H), 7.53 (d, 2H), 7.85 (d, 2H).

Ethyl 3-([5-(bromomethyl)-2-thienyl]carbonyl)amino)propionate:

To a solution of methylthiophene carboxylic acid (20 g, 0.14 mol) in DMF (30 mL) was added at 0°C carbonyldimimidazole (23 g, 0.14 mol) in portions of 10 g. After stirring at 0°C for 1 hour, a solution of ethyl 3-aminopropionate hydrochloride (21 g, 0.14 mol) in DMF (30 mL) was added followed by triethylamine (20 mL, 0.14 mol). The mixture was stirred at ambient temperature for 16 hours, filtered by suction, and the filtrate was concentrated. The residue was dissolved in ethyl acetate (100 mL), washed with water (2 x 50 mL), 1N hydrochloric

acid (2 x 50 mL), sodium bicarbonate solution (2 x 50 mL), brine (50 mL), dried (MgSO₄), and concentrated. Addition of hexane to the residue induced the crystallization of ethyl 3-({[(5-methyl-2-thienyl)carbonyl]amino}propionate (27 g, 80%).

- 5 ¹H NMR (CDCl₃): δ 1.28 (t, 3H), 2.50 (s, 3H), 2.62 (t, 2H), 3.68 (q, 2H), 4.17 (q, 2H), 6.60 (brd s, 1H), 6.66 (d, 1 H), 7.30 (d, 1H).

The above product (27 g, 0.11 mol) was dissolved in carbon tetrachloride (150 mL). *N*-bromosuccinimide (21 g, 0.12 mol) and AIBN (200 mg) was added. The mixture was refluxed
10 for 5 hours, and filtered by suction. The solid was extracted with ethyl acetate until the filtrate appeared colourless. The combined ethyl acetate extracts (200 mL) were washed with water (2 x 50 mL), dried over MgSO₄ and concentrated. The residue was recrystallized from hexane, ethyl acetate 1:1 to give ethyl 3-({[5-(bromomethyl)-2-thienyl]carbonyl}amino)propionate as a white solid (15 g, 41%).

- 15 ¹H NMR (CDCl₃): δ 1.28 (t, 3H), 2.63 (t, 2H), 3.69 (t, 2H), 4.18 (q, 2H), 4.68 (s, 2H), 7.06 (brd s, 1H), 7.07 (d, 1H), 7.32 (d, 1H).

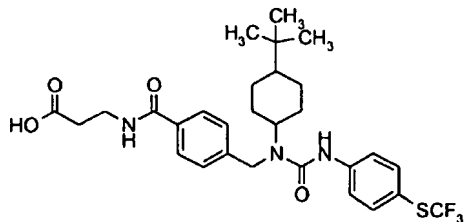
MS (APCI, neg.): 320, 318.

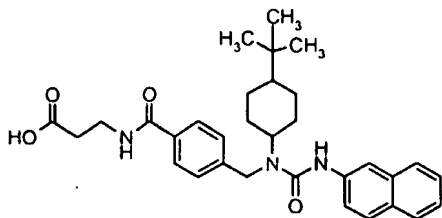
20

The following examples were prepared according to the general procedure (G).

EXAMPLE 101 (general procedure (G))

- 25 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-amino}propionic acid

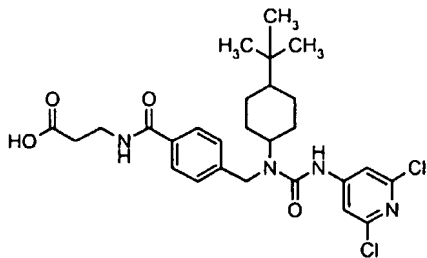


EXAMPLE 102 (general procedure (G))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-naphthalen-2-ylureidomethyl]benzoylamino}propionic acid

5

¹H NMR (DMSO-*d*₆): δ 0.83 (s, 9H), 0.91 (m, 1H), 1.11 (m, 2H), 1.40 (m, 2H), 1.67-1.76 (m, 4H), 2.44 (t, 2H), 3.44 (q, 2H), 4.10 (qt, 1H), 4.64 (s, 2H), 7.31-7.44 (m, 4H), 7.60 (dd, 1H), 7.72-7.83 (m, 5H), 7.99 (d, 1H), 8.47 (t, 1H), 8.57 (s, 1H), 12.10 (brd s, 1H).

10 MS (APCI, pos): 532.3, 531.2, 530.2, 362.3, 361.2.

EXAMPLE 103 (general procedure (G))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2,6-dichloropyridin-4-yl)ureidomethyl]benzoylamino}-propionic acid

15

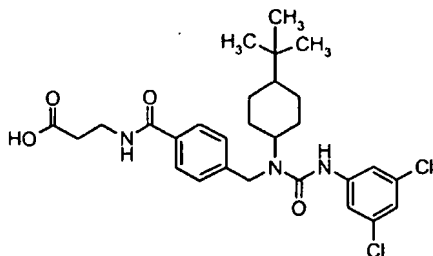
¹H NMR (DMSO-*d*₆): δ 0.81 (s, 9H), 0.91 (m, 1H), 1.07 (m, 2H), 1.39 (m, 2H), 1.63-1.74 (m, 4H), 2.49 (t, 2H), 3.44 (q, 2H), 4.10 (t, 1H), 4.61 (s, 2H), 7.29 (d, 2H), 7.66 (s, 2H), 7.76 (d, 2H), 8.47 (t, 1H), 9.21 (s, 1H), 12.10 (brd s, 1H).

20

MS (APCI, pos): 549.2, 362.2, 361.2.

EXAMPLE 104 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



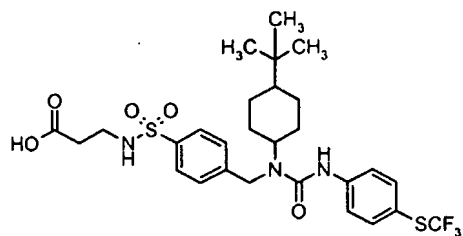
5

^1H NMR (DMSO- d_6): δ 0.82 (s, 9H), 0.90 (m, 1H), 1.05-1.15 (m, 2H), 1.40 (m, 2H), 1.65-1.75 (m, 4H), 2.51 (t, 2H), 3.44 (q, 2H), 4.00 (m, 1H), 4.59 (s, 2H), 7.12 (t, 1H), 7.30 (d, 2H), 7.62 (d, 2H), 7.75 (d, 2H), 8.45 (t, 1H), 8.69 (s, 1H), 12.50 (brd s, 1H).

10 MS (APCI, pos): 552.2, 550.2, 549.2, 548.2, 362.3, 361.2.

EXAMPLE 105 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzenesulfonylamino}propionic acid



15

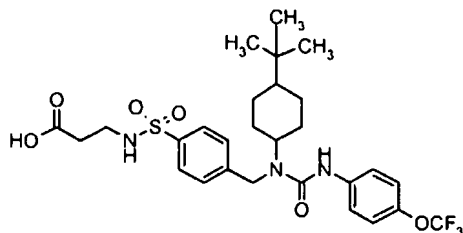
^1H NMR (Acetone- d_6): δ 0.83 (s, 9H), 0.97 (m, 1H), 1.17 (q, 2H), 1.54 (q, 2H), 1.81 (m, 4H), 2.50 (t, 2H), 3.15 (t, 2H), 4.17 (t, 1H), 4.76 (s, 2H), 6.60 (brd s, 1H), 7.56 (m, 4H), 7.67 (d, 2H), 7.83 (d, 2H), 8.19 (s, 1H).

20

MS (APCI, pos): 617.2, 616.2, 399.2, 398.1, 397.2.

EXAMPLE 106 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzenesulfonyl-
amino}propionic acid



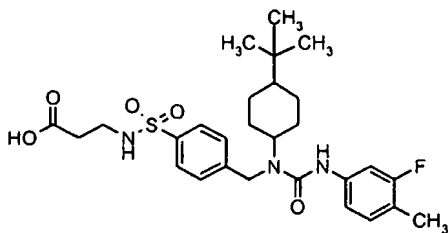
5

¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H), 1.11-1.17 (m, 3H), 1.49 (q, 2H), 1.70 (t, 4H), 2.32 (t, 2H), 2.90 (t, 2H), 4.01 (m, 2H), 4.62 (s, 2H), 7.22 (d, 2H), 7.45 (d, 2H), 7.55 (d, 2H), 7.72 (d, 2H), 8.59 (s, 1H), 12.20 (brd s, 1H).

10 MS (APCI, pos): 601.3, 600.2, 399.2, 398.3, 397.2.

EXAMPLE 107 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-fluoro-4-methylphenyl)ureidomethyl]benzenesulfonyl-
amino}propionic acid

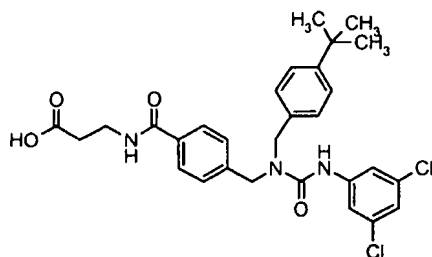


15

¹H NMR (Acetone-*d*₆): δ 0.82 (s, 6H), 0.84 (s, 3H), 1.21 (m 1H), 1.43-1.59 (m, 5H), 1.79-1.92 (m, 3H), 2.16 (s, 3H), 2.52 (t, 2H), 3.14 (q, 2H), 4.36 (m, 1H), 4.85 (s, 2H), 6.51 (btd t, 1H), 7.07 (d, 2H), 7.49-7.57 (m, 3H), 7.83-7.90 (m, 3H), 11.50 (brd s, 1H).

20

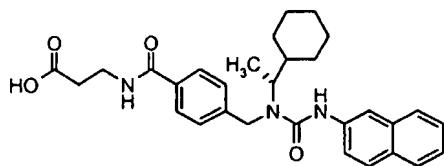
MS (APCI, pos): 548.2, 399.1, 398.3, 397.2.

EXAMPLE 108 (general procedure (G))3-{4-[1-(4-*tert*-Butylbenzyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid

- 5 ^1H NMR ($\text{DMSO}-d_6$): δ 1.25 (s, 9H), 3.33 (m, 2H), 3.43 (m, 2H), 4.51 (s, 2H), 4.63 (s, 2H), 7.14-7.17 (m, 3H), 7.30 (d, 2H), 7.36 (d, 2H), 7.66 (m, 2H), 7.79 (s, 1H), 8.50 (t, 1H), 8.97 (s, 1H), 12.25 (brd s, 1H).

MS (APCI, pos): 558.2, 557.2, 556.2, 370.1, 369.1.

10

EXAMPLE 109 (general procedure (G))3-{4-[1-((1R)-1-Cyclohexylethyl)-3-naphthalene-2-ylureidomethyl]benzoylamino}propionic acid

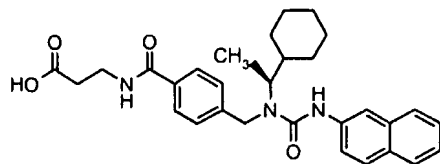
15

- ^1H NMR (CDCl_3): δ 0.92-1.10 (m, 8H), 1.36 (q, 1H), 1.59 (m, 2H), 1.67 (d, 3H), 2.51 (t, 2H), 3.54 (q, 2H), 4.05 (m, 1H), 4.30 (d, 2H), 4.50 (d, 2H), 6.32 (brd s, 2H), 6.47 (brd s, 1H), 7.00-7.07 (m, 2H), 7.23 (t, 1H), 7.27-7.30 (m, 3H), 7.54-7.67 (m, 6H).

- 20 MS (APCI, pos): 503.3, 502.3, 333.3.

EXAMPLE 110 (general procedure (G))

3-{4-[1-((1S)-1-Cyclohexylethyl)-3-naphthalene-2-ylureidomethyl]benzoylamino}propionic acid



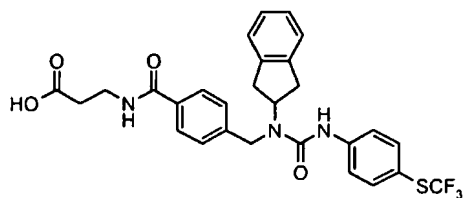
5

¹H NMR (DMSO-*d*₆): δ 0.91 (m, 3H), 1.09 (d, 3H), 1.11 (m, 3H), 1.15-1.88 (m, 6H), 2.44 (t, 2H), 3.34 (q, 2H), 4.09 (q, 1H), 4.36 (d, 1H), 4.80 (d, 1H), 7.32 (t, 1H), 7.38 (d, 2H), 7.42 (t, 1H), 7.55 (dd, 1H), 7.71-7.79 (m, 5H), 7.97 (dd, 1H), 8.52 (t, 1H).

10 MS (APCI, pos): 502.2, 353.0.

EXAMPLE 111 (general procedure (G))

3-{4-[1-(2,3-Dihydro-1H-inden-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

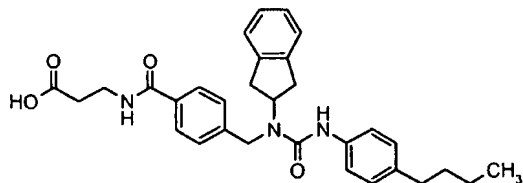


15

¹H NMR (DMSO-*d*₆): δ 2.44 (t, 2H), 2.90-3.06 (m, 4H), 3.40-3.46 (m, 2H), 4.67 (s, 2H), 5.09 (qt, 1H), 7.06-7.21 (m, 4H), 7.29 (d, 2H), 7.52 (d, 2H), 7.68 (d, 2H), 7.77 (d, 2H), 8.48 (t, 1H), 8.88 (s, 1H), 12.00 (brd s, 1H).

20

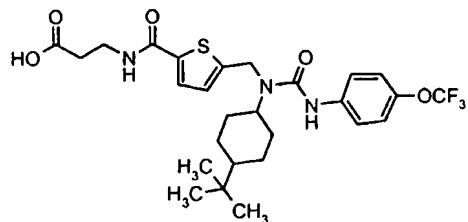
MS (APCI, pos): 558.2, 339.1.

EXAMPLE 112 (general procedure (G))3-{4-[1-(2,3-Dihydro-1*H*-inden-2-yl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid

5

¹H NMR (DMSO-*d*₆): δ 0.87 (t, 3H), 1.28 (hex, 2H), 1.49 (qt, 2H), 2.51 (t, 2H), 2.69 (t, 2H), 2.95 (d, 1H), 3.01 (d, 1H), 3.25 (d, 1H), 3.30 (d, 1H), 3.70 (q, 2H), 4.59 (s, 2H), 5.21 (qt, 1H), 6.21 (s, 1H), 6.91 (t, 1H), 7.02 (s, 4H), 7.18 (s, 4H), 7.37 (d, 2H), 7.47 (d, 2H).

10 MS (APCI, pos): 514.2, 339.1.

EXAMPLE 113 (general procedure (G))3-{5-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carbonylamino}propionic acid

15

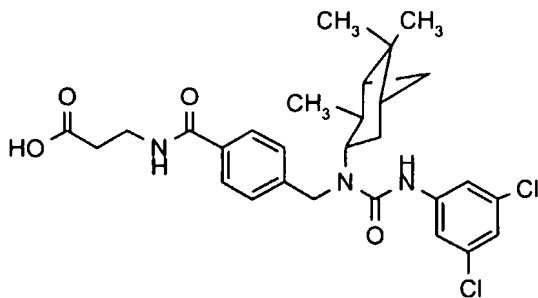
¹H NMR (DMSO-*d*₆): δ 0.61 (s, 9H), 0.73 (m, 1H), 0.87 (q, 2H), 1.24 (q, 2H), 1.51 (m, 4H), 2.21 (t, 2H), 3.16 (q, 2H), 3.73 (t, 1H), 4.42 (s, 2H), 6.77 (d, 1H), 7.02 (d, 2H), 7.29 (d, 2H), 7.33 (d, 1H), 8.21 (t, 1H), 8.37 (s, 1H), 11.99 (brd s, 1H).

20

MS (APCI, neg): 568.0, 569.0.

EXAMPLE 114 (general procedure (G))

3-{4-[1-((2R,3R)-2,6,6-Trimethylbicyclo[3.3.1]hept-3-yl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid



5

$^1\text{H NMR}$ ($\text{DMSO}-d_6$): δ 0.96 (d, 3H), 1.07 (s, 3H), 1.18 (s, 3H), 1.65-1.71 (m, 2H), 1.89-1.94 (m, 2H), 2.20-2.28 (m, 2H), 2.44 (t, 2H), 3.49 (q, 2H), 4.66 (s, 2H), 4.85 (m, 1H), 7.10 (t, 1H), 7.30 (d, 2H), 7.53 (d, 2H), 7.80 (d, 2H), 8.47 (t, 1H), 8.69 (s, 1H).

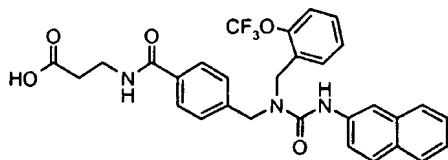
10 MS (APCI, pos): 546.1, 359.2, 287.1.

The following examples 115 to 136 were all found to displace more than 50% of the glucagon tracer when screened at 1 μM concentration in the glucagon binding assay II. These compounds are all expected to be present in the library.

15

EXAMPLE 115 (general procedure (G))

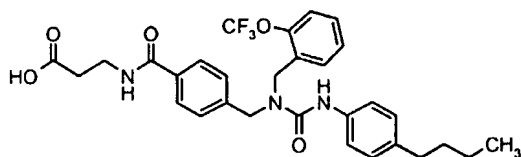
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-naphthalene-2ylureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 116 (general procedure (G))

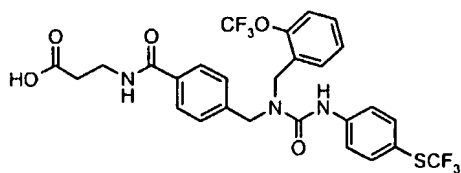
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 117 (general procedure (G))

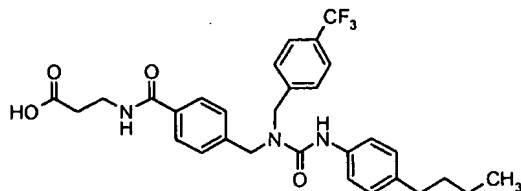
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



15

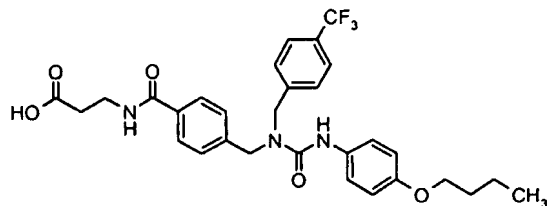
EXAMPLE 118 (general procedure (G))

3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid



EXAMPLE 119 (general procedure (G))

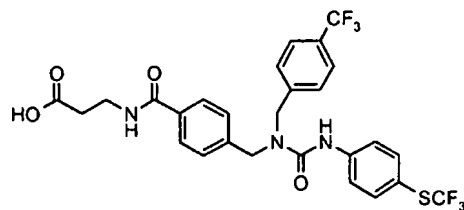
3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-butoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 120 (general procedure (G))

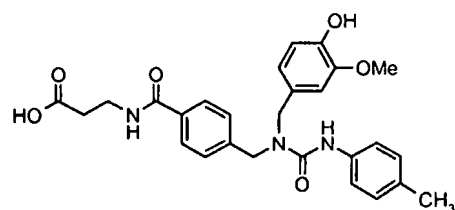
3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 121 (general procedure (G))

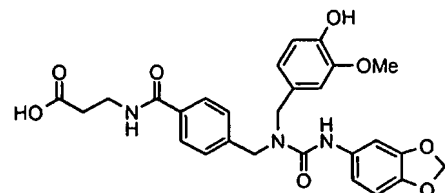
3-{4-[1-(4-Hydroxy-3-methoxybenzyl)-3-(4-methylphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 122 (general procedure (G))

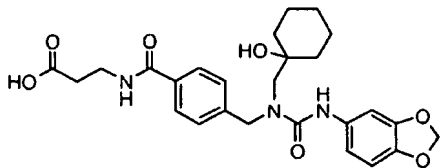
3-{4-[1-(4-Hydroxy-3-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)ureidomethyl]benzoylamino}propionic acid



20

EXAMPLE 123 (general procedure (G))

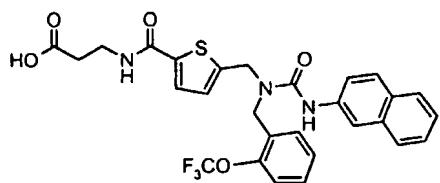
3-{4-[1-(1-Hydroxycyclohexylmethyl)-3-(3,4-methylenedioxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



5

EXAMPLE 124 (general procedure (G))

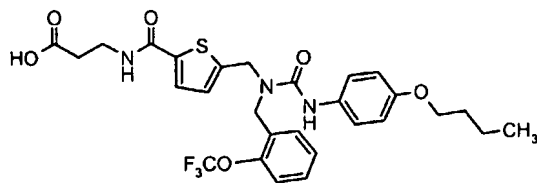
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonyl-amino}propionic acid



10

EXAMPLE 125 (general procedure (G))

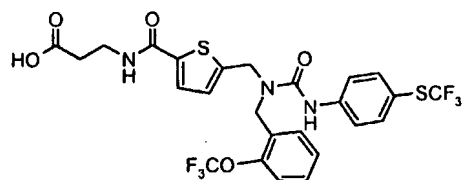
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-(4-butoxyphenyl)ureidomethyl]thiophene-2-carbonyl-amino}propionic acid



15

EXAMPLE 126 (general procedure (G))

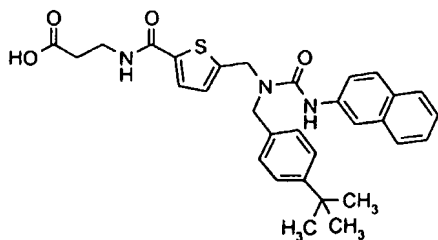
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-(4-trifluoromethylsulfonylphenyl)ureidomethyl]-thiophene-2-carbonylamino}propionic acid



20

EXAMPLE 127 (general procedure (G))

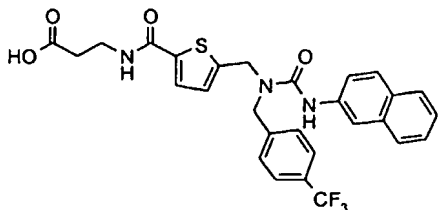
3-{5-[1-(4-*tert*-Butylbenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonylamino}-propionic acid



5

EXAMPLE 128 (general procedure (G))

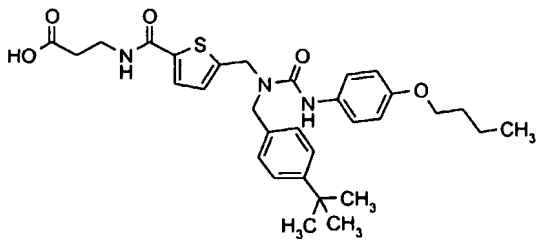
3-{5-[1-(4-Trifluoromethylbenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonylamino}propionic acid



10

EXAMPLE 129 (general procedure (G))

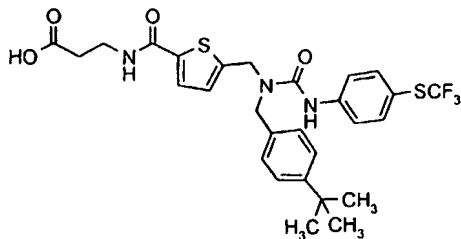
3-{5-[1-(4-*tert*-Butylbenzyl)-3-(4-butoxyphenyl)ureidomethyl]thiophene-2-carbonylamino}-propionic acid



15

EXAMPLE 130 (general procedure (G))

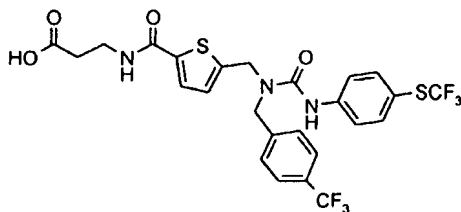
3-{5-[1-(4-*tert*-Butylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]thiophene-2-carboxylamino}propionic acid



5

EXAMPLE 131 (general procedure (G))

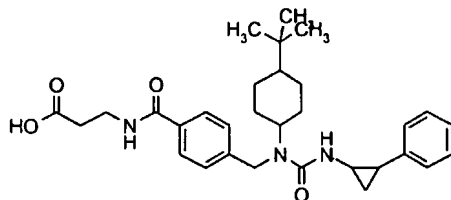
3-{5-[1-(4-Trifluoromethylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]thiophene-2-carboxylamino}propionic acid



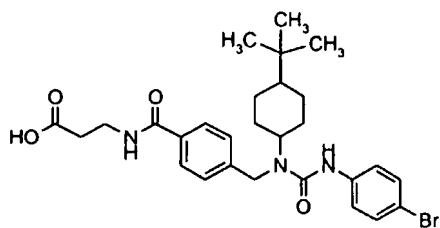
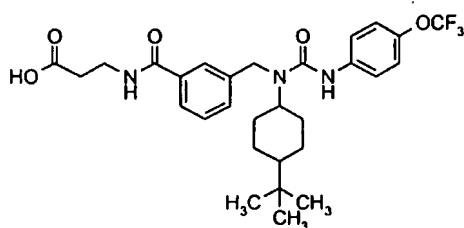
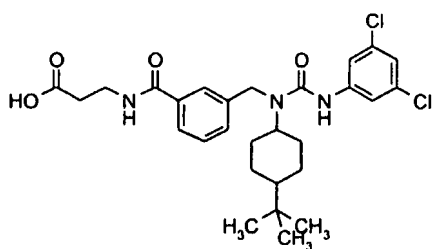
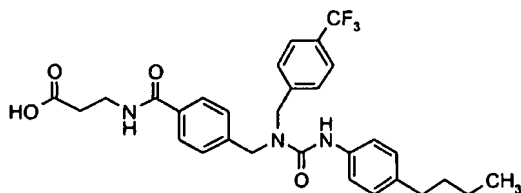
10

EXAMPLE 132 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-phenylcyclopropyl)ureidomethyl]benzoylamino}propionic acid

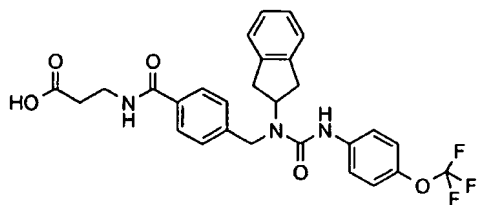


15

EXAMPLE 133 (general procedure (G))**3-{4-[3-(4-Bromophenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid****5 EXAMPLE 134 (general procedure (G))****3-{3-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid****10 EXAMPLE 135 (general procedure (G))****3-{3-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid****15 EXAMPLE 136 (general procedure (G))****3-{4-[3-(4-Butylphenyl)-1-(4-trifluoromethylbenzyl)ureidomethyl]benzoylamino}propionic acid**

EXAMPLE 137 (general procedure (G))

3-{4-[1-(1-Indan-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



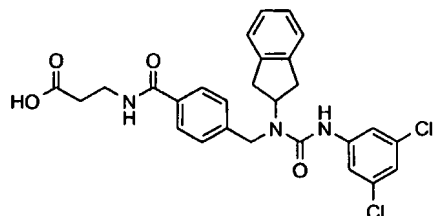
- 5 ^1H NMR (DMSO- d_6): δ 2.52 (t, 2H), 2.97 (m, 4H), 3.47 (qt, 2H), 4.72 (s, 2H), 7.09 – 7.20 (m, 4H), 7.24 (d, 2H), 7.29 (d, 2H), 7.57 (d, 2H), 7.77 (d, 2H), 8.48 (brd t, 1H), 8.73 (brd s, 1H), 12.21 (brd s, 1H).

MS (APCI, pos): 542.2, 543.2, 339.1.

10

EXAMPLE 138 (general procedure (G))

3-{4-[1-(1-Indan-2-yl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



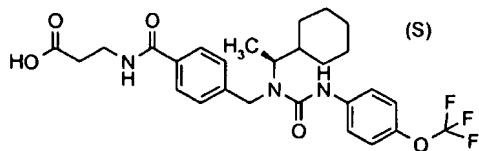
- 15 ^1H NMR (DMSO- d_6): δ 2.51 (t, 2H), 2.95 – 2.99 (m, 4H), 3.45 (qt, 2H), 4.71 (s, 2H), 7.09 – 7.18 (m 5H), 7.28 (d, 2H), 7.64 (s, 2H), 7.78 (d, 2H), 8.49 (t, 1H), 8.86 (s, 1H), 12.21 (brd s, 1H).

MS (APCI, pos): 526.1, 339.1.

20

EXAMPLE 139 (general procedure (G))

3-{4-[1-((1S)-1-Cyclohexylethyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



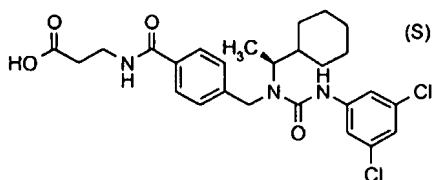
5

^1H NMR ($\text{DMSO}-d_6$): δ 0.84 – 1.19 (m, 8H), 1.47 – 1.70 (m, 6H), 1.88 (t, 2H), 3.16 (qt, 2H), 4.03 (quintet, 1H), 4.33 (d, 1H), 4.78 (d, 1H), 7.10 (d, 2H), 7.50 (d, 2H), 7.70 (d, 2H), 8.62 (brd s, 1H), 8.95 (brd t, 1H).

10 MS (APCI, pos): 536.2, 537.2, 538.2.

EXAMPLE 140 (general procedure (G))

3-{4-[1-((1S)-1-Cyclohexylethyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



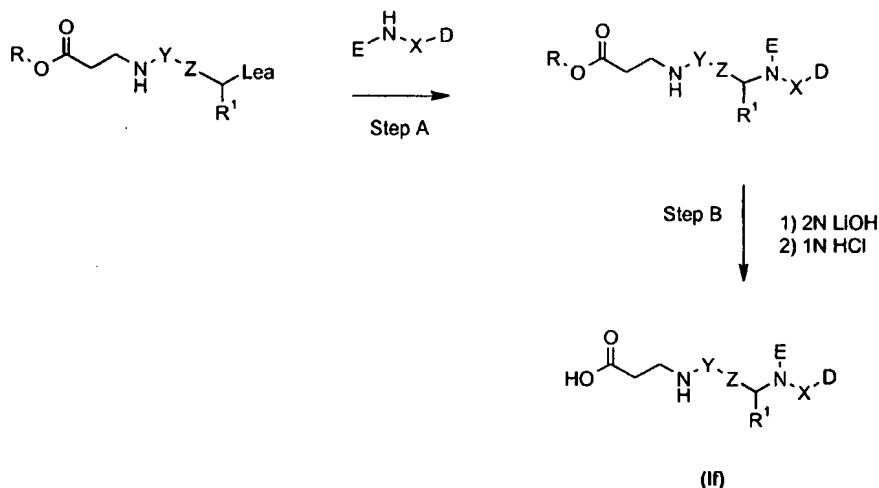
15

^1H NMR (CDCl_3): δ 1.16 – 1.27 (m, 8H), 1.40 (m, 1H), 1.69 – 1.80 (m, 5H), 2.68 (t, 2H), 3.70 (qt, 2H), 4.20 (m, 1H), 4.43 (dd, 2H), 6.44 (brd s, 1H), 6.94 (m, 2H), 7.17 (s, 2H), 7.36 (d, 2H), 7.74 (d, 2H).

20

MS (APCI, pos): 520.2, 522.1, 333.2.

General procedure (H) for the solution phase synthesis of compounds of the general formula (If):



5

wherein

R^1 , E, Z and D are as defined for formula (I),

10 X is $-(CH_2)_q-$, wherein q is as defined for formula (I),

Y is $-C(O)-$ or $-S(O)_2-$,

R is C_{1-6} -alkyl and

15

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl.

The preparation of starting materials are as described above in procedure (G).

20 Library solution phase synthesis (procedure (H)) of compounds of the general formula (If):

Step A:

The appropriate alkylhalide (0.02 mmol) in DMF was added into the wells of a deepwell plate containing the appropriate amine ($E-NH-X-D$) (0.02 mmol) and solid potassium carbonate (2 eq) in DMF. The mixtures were agitated at $55^\circ C$ for 16 hours to give the alkylated product.

25

Step B:

To the crude product from step A was added aqueous 2M LiOH (4 eq). The mixtures are agitated for at least four hours before they are filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

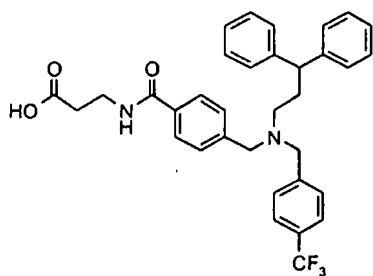
5

The following examples 141 to 152 were prepared according to the general procedure (H). They were all found to displace more than 50% of the glucagon tracer when screened at 1 μ M concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

10

EXAMPLE 141 (general procedure (H))

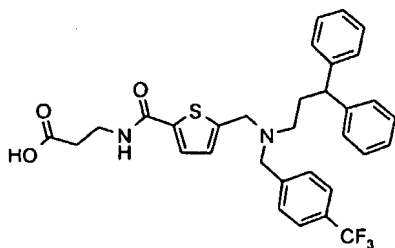
3-(4-(((3,3-Diphenylpropyl)-(4-trifluoromethylbenzyl)amino)methyl)benzoylamino)propionic acid



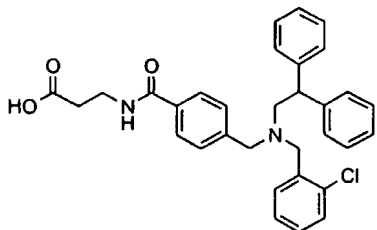
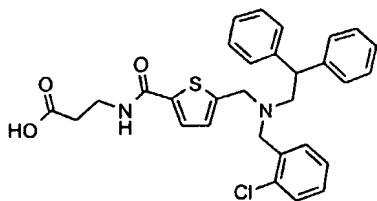
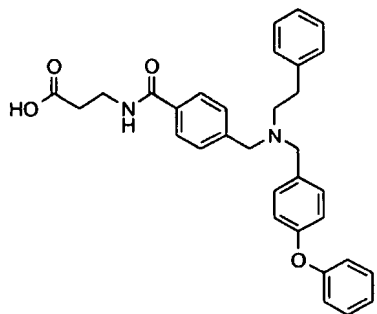
15

EXAMPLE 142 (general procedure (H))

3-(5-(((3,3-Diphenylpropyl)-(4-trifluoromethylbenzyl)amino)methyl)thiophene-2-carbonylamino)propionic acid

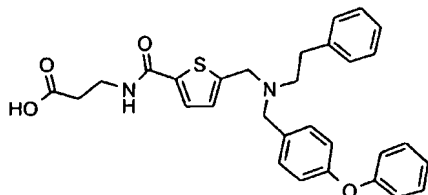


20

EXAMPLE 143 (general procedure (H))3-(4-(((2,2-Diphenylethyl)-(2-chlorobenzyl)amino)methyl)benzoylamino)propionic acid5 EXAMPLE 144 (general procedure (H))3-(5-(((2,2-Diphenylethyl)-(2-chlorobenzyl)amino)methyl)thiophene-2-carbonylamino)-propionic acid10 EXAMPLE 145 (general procedure (H))3-(4-(((2-Phenylethyl)-(4-phenoxybenzyl)amino)methyl)benzoylamino)propionic acid

EXAMPLE 146 (general procedure (H))

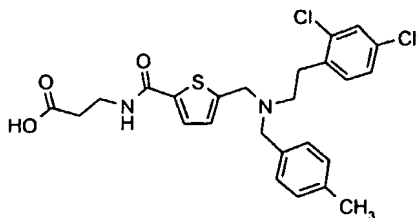
3-(5-(((2-Phenylethyl)-(4-phenoxybenzyl)amino)methyl)thiophene-2-carboxylamino)propionic acid



5

EXAMPLE 147 (general procedure (H))

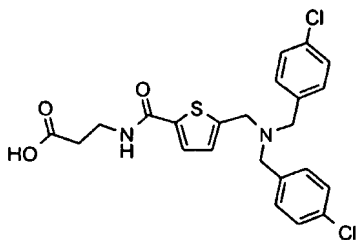
3-(5-(((2,4-Dichlorophenethyl)-(4-methylbenzyl)amino)methyl)thiophene-2-carboxylamino)propionic acid

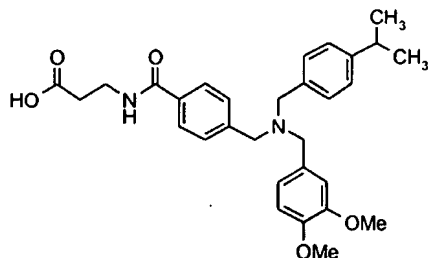


10

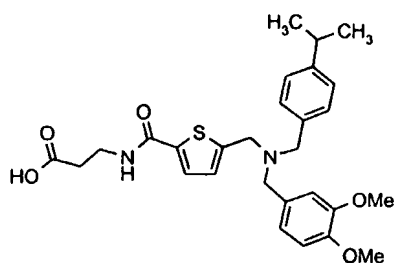
EXAMPLE 148 (general procedure (H))

3-(5-([Bis-(4-chlorobenzyl)amino)methyl]thiophene-2-carboxylamino)propionic acid

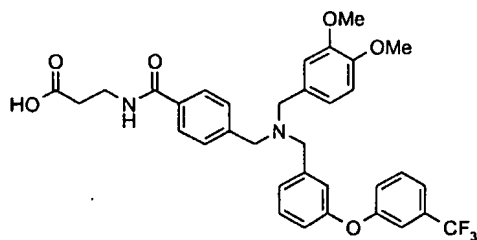


EXAMPLE 149 (general procedure (H))**3-(4-(((3,4-Dimethoxybenzyl)-(4-isopropylbenzyl)amino)methyl)benzoylamino)propionic acid**

5

EXAMPLE 150 (general procedure (H))**3-(5-(((3,4-Dimethoxybenzyl)-(4-isopropylbenzyl)amino)methyl)thiophene-2-carbonylamino)-propionic acid**

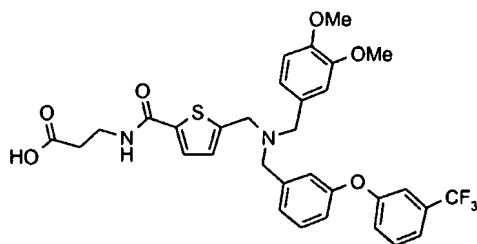
10

EXAMPLE 151 (general procedure (H))**3-(4-(((3,4-Dimethoxybenzyl)-(3-[3-trifluoromethylphenoxy]benzyl)amino)methyl)benzoylamino)propionic acid**

15

EXAMPLE 152 (general procedure (H))

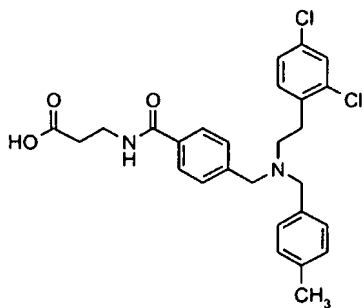
3-(5-((3,4-Dimethoxybenzyl)-(3-[3-trifluoromethoxy]benzyl)amino)methyl)thiophene-2-carboxylamino)propionic acid



5

EXAMPLE 153 (general procedure (H))

3-(4-((2,4-Dichlorophenethyl)-(4-methylbenzyl)amino)methyl)benzoylamino)propionic acid

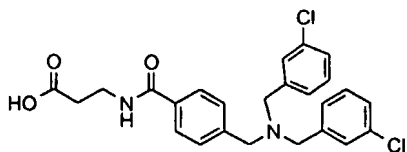


10 ^1H NMR (MeOH- d_4): δ 2.38 (s, 3H), 2.64 (t, 2H), 3.10 (m, 4H), 3.50 (qt, 2H), 4.40 (s, 2H), 4.50 (s, 2H), 7.20 (m, 4H), 7.40 (m, 3H), 7.50 (d, 2H), 7.90 (d, 2H), 8.60 (t, 1H).

MS (APCI, pos): 499.1, 500.2, 501.2.

15 EXAMPLE 154 (general procedure (H))

3-(4-((Bis-(3-chlorobenzyl)amino)methyl)benzoylamino)propionic acid

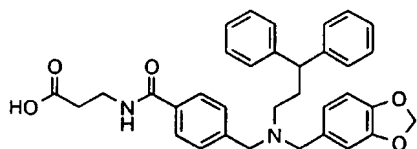


20 ^1H NMR (CDCl₃): δ 2.70 (t, 2H), 3.40 (s, 4H), 3.50 (s, 2H), 3.70 (qt, 2H), 6.9 (t, 1H), 7.20 (m, 6H), 7.30 (s, 2H), 7.40 (d, 2H), 7.70 (d, 2H).

MS (APCI, pos): 471.0, 472.0, 473.0.

EXAMPLE 155 (general procedure (H))

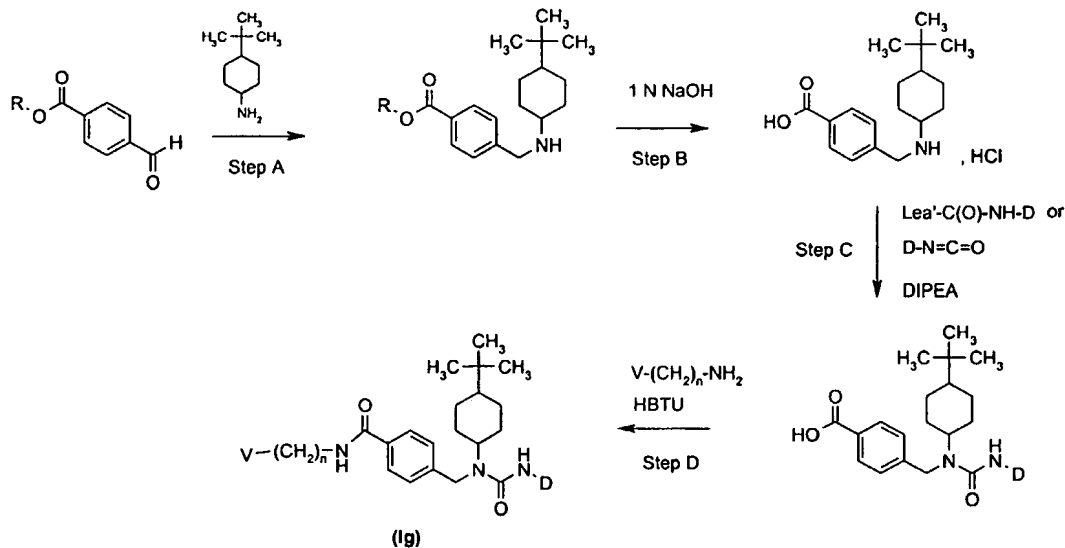
3-(4-((3,3-Diphenylpropyl)-(3,4-methylenedioxybenzyl)amino)methyl)benzoylamino)propionic acid



^1H NMR (CD_3CN): δ 2.46 – 2.54 (m, 2H), 2.63 (t, 2H), 2.82 – 2.88 (m, 2H), 3.61 (qt, 2H), 3.86 (t, 1H), 4.20 – 4.40 (m, 4H), 6.02 (s, 2H), 6.83 (d, 1H), 6.90 (d, 1H), 6.97 (s, 1H), 7.16 – 7.29 (m, 10H), 7.50 (d, 2H), 7.77 (d, 2H).

MS (APCI, pos): 551.2, 552.2, 553.2.

General procedure (I) for the solution phase synthesis of compounds of the general formula (Ig):



wherein

n, D and V are as defined for formula (I),

R is C₁₋₆-alkyl and

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy.

5 Step A:

To a solution of ethyl 4-formylbenzoate (6 g, 33.7 mmol) in DMF was added 4-*tert*-butylcyclohexylamine (5.8 g, 37.1 mmol), sodium cyanoborohydride (3.2 g, 50.6 mmol) and a catalytic amount of TFA. The solution was stirred at room temperature for 5 hours. The reaction was diluted with ethyl acetate and washed with aqueous sodium bicarbonate (3x), brine (3x),
10 dried over MgSO₄, and concentrated to a syrup. The desired secondary amine was purified by silica gel column chromatography using ethyl acetate.

¹H NMR (DMSO-*d*₆): δ 0.78 (s, 9H), 0.91 (brd m, 5H), 1.30 (t, 3H), 1.67 (brd m, 2H), 1.93 (brd m, 2H), 2.21 (1H), 3.77 (s, 2H), 4.30 (qt, 2H), 7.44 (d, 2H), 7.87 (d, 2H).

15

Step B:

To a solution of the above benzoate in THF/MeOH (3/1) was added aqueous 1M NaOH. After stirring the reaction at room temperature for 15 minutes, the solution was made acidic with 1N HCl. The product was extracted with ethyl acetate (3x) and washed with brine (3x),
20 dried over MgSO₄, and concentrated to a solid. The carboxylic acid product was recrystallized from dichloromethane as the hydrochloride salt.

¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H), 0.97 (m, 3H), 1.44 (qt, 2H), 1.81 (m, 2H), 2.17 (m, 2H), 2.90 (brd m, 1H), 4.20 (t, 2H), 7.73 (d, 2H), 7.95 (d, 2H), 9.52 (s, 2H), 12.60 (brd s, 1H).

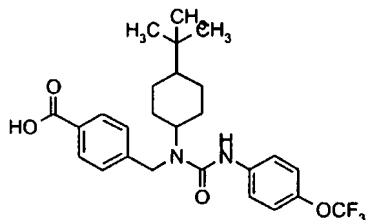
25

Step C:

To a solution of the amine in DMF was added the desired isocyanate (1.1 eq) or alternatively Lea'-C(O)-NH-D, and the reaction was stirred at room temperature for 10 minutes. When using Lea'-C(O)-NH-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was also added. The solvent was concentrated to an oil. The residue was suspended in ethyl acetate and upon sitting in cold, the desired urea crystallized as a white solid.
30

Examples of products prepared in this fashion are shown below.

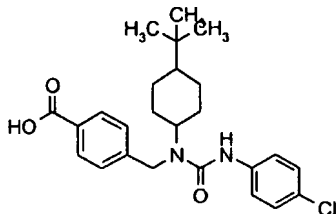
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid



5

^1H NMR (DMSO- d_6): δ 0.81 (brd s, 9H), 1.12 (qt, 2H), 1.37 (qt, 2H), 1.69 (t, 4H), 4.06 (t, 1H), 4.62 (s, 2H), 7.21 (d, 2H), 7.35 (d, 2H), 7.54 (d, 2H), 7.87 (d, 2H), 8.57 (s, 1H), 12.84 (brd s, 1H).

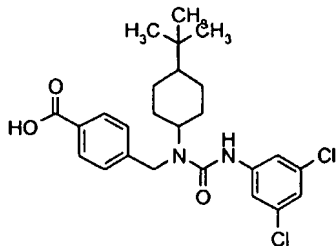
10 4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoic acid



^1H NMR (DMSO- d_6): δ 0.82 (s, 9H), 0.91 (m, 1H), 1.15 (qt, 2H), 1.37 (qt, 2H), 1.69 (t, 4H), 4.04 (m, 1H), 4.61 (s, 2H), 7.26 (d, 2H), 7.35 (d, 2H), 7.47 (d, 2H), 7.86 (d, 2H), 8.49 (s, 1H), 12.83 (brd s, 1H).

15

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoic acid



20 ^1H NMR (DMSO- d_6): δ 0.81 (s, 9H), 0.92 (m, 1H), 1.14 (qt, 2H), 1.47 (qt, 2H), 1.69-1.72 (m, 4H), 4.04 (m, 1H), 4.61 (s, 2H), 7.12 t, 1H), 7.35 (d, 2H), 7.63 (d, 2H), 7.88 (d, 2H), 8.87 (s, 1H), 12.95 (brd s, 1H).

Step D:

This step was carried out in a combinatorial fashion in solution.

- 5 To a solution of one of the above benzoic acids (0.02 mmol) in a suitable solvent such as CH₂Cl₂, DMF, or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before the amine (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure to afford the crude product.

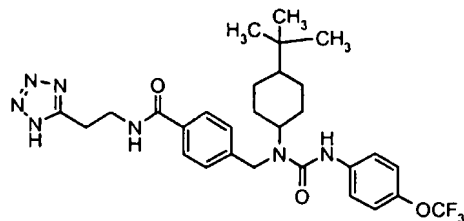
10

The following examples were prepared according to the general procedure (I).

EXAMPLE 156 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-[2-(1*H*-tetrazol-5-yl)ethyl]benzamide

15



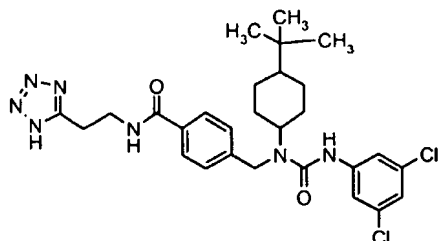
- ¹H NMR (DMSO-*d*₆): δ 0.81 (s, 9H), 0.90 (m, 1H), 1.11 (qt, 2H), 1.41 (qt, 2H), 1.70 (m, 4H), 3.13 (t, 2H), 3.60 (qt, 2H), 4.05 (quintet, 1H), 4.60 (s, 2H), 7.22 (d, 2H), 7.31 (d, 2H), 7.55 (d, 2H), 7.73 (d, 2H), 8.54 (s, 1H), 8.56 (t, 1H).

20

MS (APCI, pos): 588.3.

EXAMPLE 157 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-[2-(1*H*-tetrazol-5-yl)ethyl]benzamide



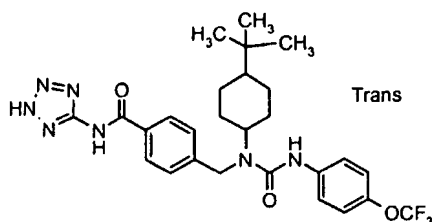
5

¹H NMR (MeOH-*d*₄): δ 0.87 (s, 9H), 1.01 (m, 1H), 1.25 (m, 2H), 1.46 (q, 2H), 1.83 (t, 4H), 3.27 (t, 2H), 3.78 (t, 2H), 4.10 (m, 1H), 4.67 (s, 2H), 7.04 (t, 1H), 7.38 (d, 2H), 7.43 (t, 2H), 7.75 (d, 2H), 8.44 (brd s, 1H).

10 MS (APCI, pos): 480.2, 478.2, 477.2, 435.1, 433.2, 290.1, 156.2.

EXAMPLE 158 (general procedure (I))

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



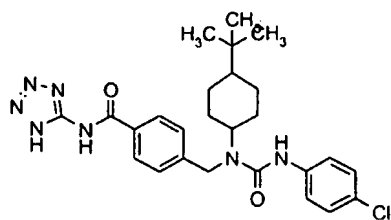
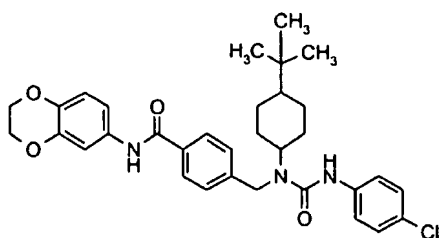
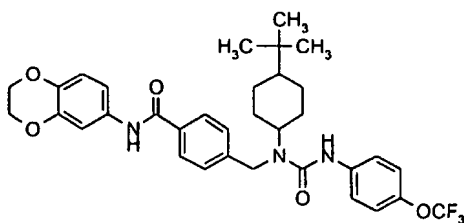
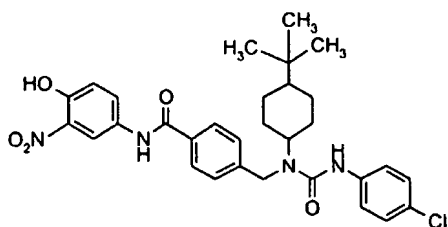
15

¹H NMR (MeOH-*d*₄): δ 0.86 (s, 9H), 1.01 (m, 1H), 1.22 (qt, 2H), 1.48 (qt, 2H), 1.85 (m, 4H), 4.11 (m, 1H), 4.70 (s, 2H), 7.16 (d, 2H), 7.42 (d, 2H), 7.46 (d, 2H), 7.99 (d, 2H).

20 MS (APCI, pos): 560.2, 561.2, 357.1, 358.2.

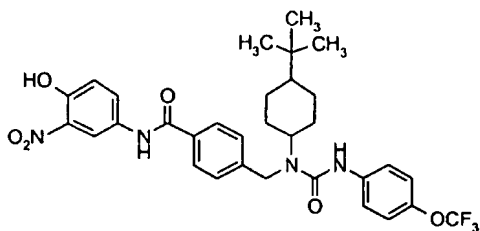
The following examples 159 to 171 were all found to displace more than 50% of the glucagon tracer when screened at 1 μM concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

25

EXAMPLE 159 (general procedure (I))**4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(1*H*-tetrazol-5-yl)benzamide****5 EXAMPLE 160 (general procedure (I))****4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide****10 EXAMPLE 161 (general procedure (I))****4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide****15 EXAMPLE 162 (general procedure (I))****4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)benzamide**

EXAMPLE 163 (general procedure (I))

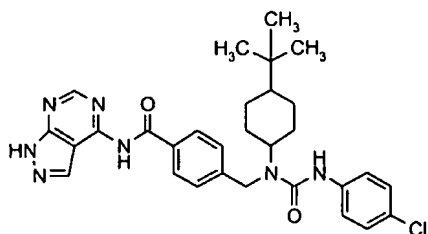
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)benzamide



5

EXAMPLE 164 (general procedure (I))

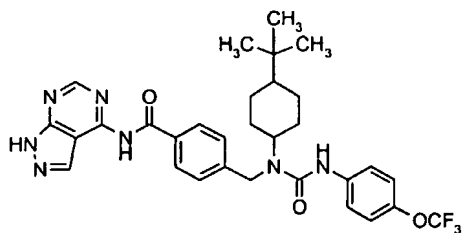
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)benzamide



10

EXAMPLE 165 (general procedure (I))

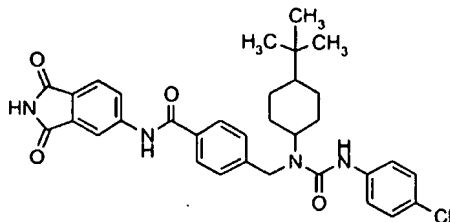
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)benzamide



15

EXAMPLE 166 (general procedure (I))

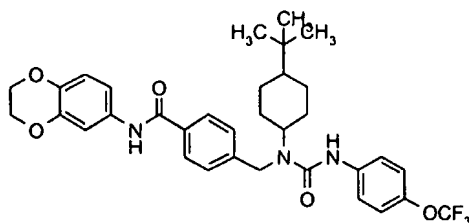
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)benzamide



5

EXAMPLE 167 (general procedure (I))

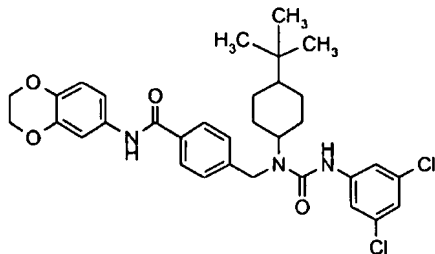
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



10

EXAMPLE 168 (general procedure (I))

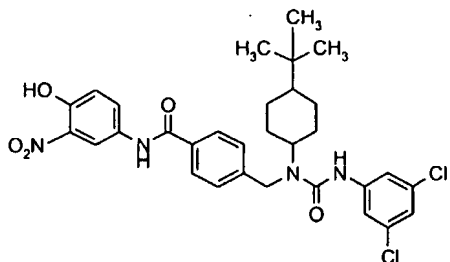
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



15

EXAMPLE 169 (general procedure (I))

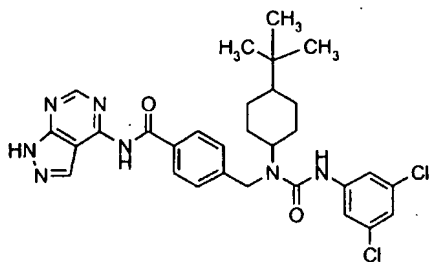
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)-benzamide



5

EXAMPLE 170 (general procedure (I))

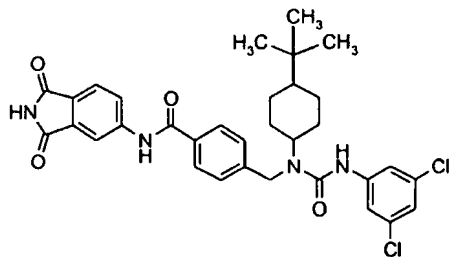
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-yl)benzamide



10

EXAMPLE 171 (general procedure (I))

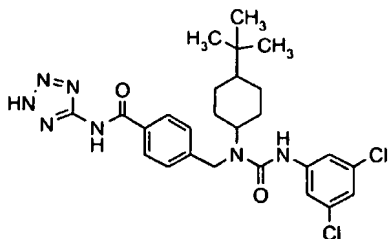
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)benzamide



15

EXAMPLE 172 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



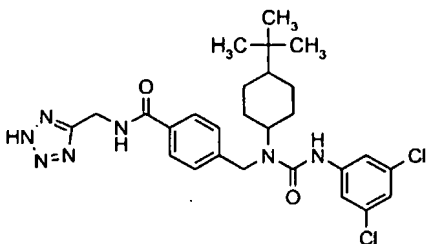
5

¹H NMR (MeOH-*d*₄): δ 0.92 (s, 9H), 1.01 (m, 1H), 1.18 – 1.31 (m, 2H), 1.44 – 1.52 (m, 2H), 1.80 – 1.87 (m, 4H), 4.12 (m, 1H), 4.72 (s, 2H), 7.05 (t, 1H), 7.46 (d, 2H), 7.49 (d, 2H), 8.02 (d, 2H).

10 MS (APCI, pos): 544.2, 357.2.

EXAMPLE 173 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-ylmethyl)-benzamide



15

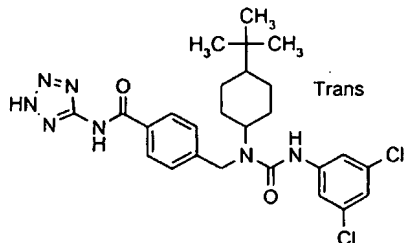
¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H), 0.92 (d, 1H), 1.04 – 1.20 (m, 2H), 1.42 (qt, 2H), 1.70 (m, 4H), 4.05 (qt, 1H), 4.61 (s, 2H), 4.73 (d, 2H), 7.12 (s, 1H), 7.34 (d, 2H), 7.62 (s, 2H), 7.83 (d, 2H), 8.70 (s, 1H), 9.18 (t, 1H).

20

MS (APCI, pos): 558.2, 560.2, 372.2, 343.2.

EXAMPLE 174 (general procedure (I))

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

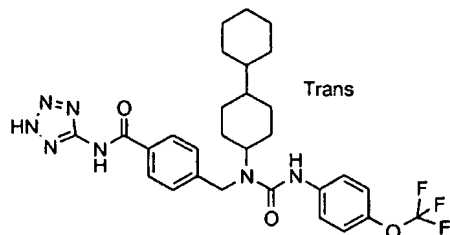
^1H NMR (DMSO- d_6): δ 0.82 (s, 9H), 1.01 (m, 1H), 1.10 (m, 2H), 1.42 (m, 2H), 1.74 (m, 4H), 4.40 (m, 1H), 4.63 (s, 2H), 7.13 (s, 1H), 7.39 (d, 2H), 7.63 (s, 2H), 8.01 (d, 2H), 8.73 (s, 1H).

MS (APCI, neg): 542.1, 544.1.

10

EXAMPLE 175 (general procedure (I))

4-[1-(*trans*-4-Cyclohexylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

trans-4-Cyclohexylcyclohexylamine was prepared according to H. Booth, G. C. Gidley, P. R. Thornburrow, J. Chem. Soc. B, 1971, 1047-50.

The *cis* isomer may be prepared by reductive amination of cyclohexylcyclohexyl ketone with the appropriate amine followed by column chromatographic separation of the *cis/trans* isomers.

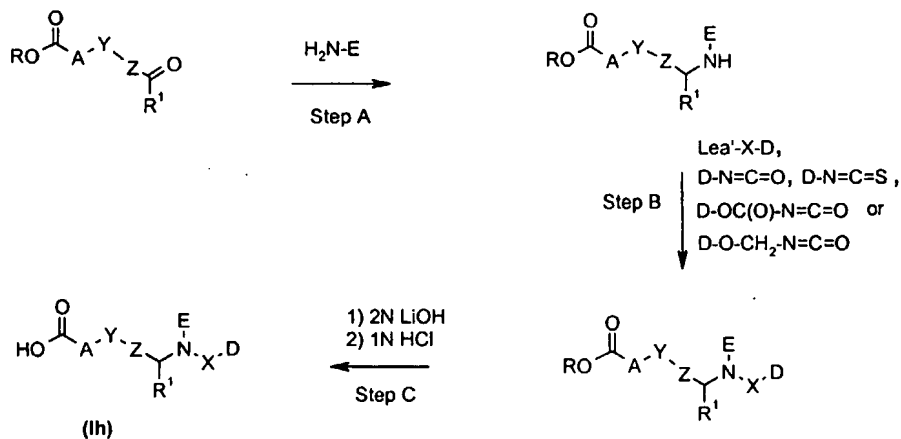
^1H NMR (DMSO- d_6): δ 0.82 – 1.10 (m, 10H), 1.60 (m, 2H), 1.64 – 1.80 (m, 8H), 4.03 (quintet, 1H), 4.64 (s, 2H), 7.22 (d, 2H), 7.41 (d, 2H), 7.54 (d, 2H), 8.03 (d, 2H), 8.56 (s, 1H), 12.32 (s, 1H), 15.90 (brd s, 1H).

25

MS (APCI, pos): 586.1, 587.2, 383.2, 384.2.

General procedure (J) for the solution phase synthesis of compounds of the general formula (Ih):

5



wherein

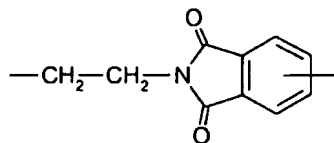
10 R^1 , E and D are as defined for formula (I),

X is $-\text{C(O)NH-}$, $-\text{C(O)NH-CH}_2\text{-O-}$, $-\text{C(O)NH-C(O)O-}$ or $-\text{C(S)NH-}$,

15 $-\text{A-Y-}$ is $-(\text{CH})_2\text{-NH-C(O)-}$ or $-(\text{CH}_2)_n\text{-O-}$, wherein n is as defined for formula (I), and Z is as defined for formula (I),

or

$-\text{A-Y-Z-}$ together is



20

R is C_{1-6} -alkyl and

Lea' is a leaving group such as $-\text{OSu}$, chloro, phenoxy or 4-nitrophenoxy.

Step A:

The appropriate aldehyde (0.011 mmol) in CH_2Cl_2 was dispensed into the wells of a deepwell plate containing the desired amines in CH_2Cl_2 . To this solution was added sodium triacetoxy-
5 borohydride (1.5 eq) followed by a catalytic amount of acetic acid. The reaction was left to proceed for 15 hours.

Step B:

To the resulting amines from step A was added the desired isocyanate or isothiocyanate or
10 alternatively Lea'-X-D (0.011 mmol) in CH_2Cl_2 . When using Lea'-X-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was also added. The reactions were agitated for three hours and the solvents were removed under reduced pressure to give the desired ureas or thioureas.

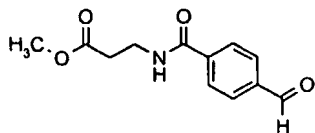
Step C:

The residue obtained in step B was dissolved in DMF and aqueous 2 M lithium hydroxide (10 eq.) was added into each reaction well. The samples were shaken overnight and filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

General preparation of formylarylcarboxamides as starting materials:

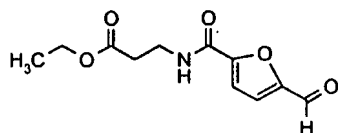
The formylarylcarboxamides were prepared from the coupling of the corresponding oxo-arylcarboxylic acid and the methyl or ethyl-3-aminopropionate hydrochloride according to the procedure described below.

25 To a solution of the formylarylcarboxylic acid in a suitable solvent such as CH_2Cl_2 , DMF, or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before ethyl or methyl-3-aminopropionate hydrochloride (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1N HCl. The
30 organic layer was separated and washed with H_2O (2x), aqueous NaHCO_3 (3x), brine (2x), dried over MgSO_4 and concentrated to give the desired product.

Methyl 3-[(4-formylbenzoyl)amino]propionate:

¹H NMR (DMSO-*d*₆): δ 2.62 (t, 2H), 3.52 (q, 2H), 3.60 (s, 3 H), 8.00 (m, 4 H), 8.98 (t, 1 H),
5 10.06 (s, 1H).

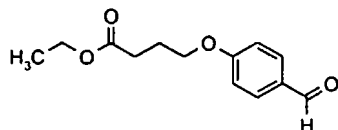
MS (APCI, neg.): 234.0, 147.9

Ethyl 3-[(5-formyl-2-furoyl)aminopropionate:

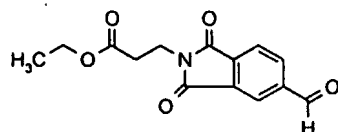
10

¹H NMR (DMSO-*d*₆): δ 1.67 (t, 3H), 2.57 (t, 2H), 3.48 (q, 2H), 4.08 (q, 2H), 7.29 (d, 1H), 7.59
(d, 1H), 8.83 (brd t, 1H), 9.69 (s, 1H).

15 MS (APCI, pos.): 240.1, 194.1, 152.0.

Ethyl 4-(4-formylphenoxy)butyrate:

20 This compound was prepared according to D. R. Buckle, A. E. Fenwick, D. J. Outred, C. J. M. Rockwell, J. Chem. Res. Miniprint 12 (1987) 3144-3177.

Ethyl 3-[5-formyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate:

25

Step 1: Ethyl 3-[5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

A solution of 4-methylphthalic anhydride (21.3 g, 0.13 mol), ethyl 3-aminopropionate hydrochloride (20.2 g, 0.13 mol), and triethylamine (19 mL) in NMP was stirred at ambient temperature for 3 days, and heated to 130°C for 3 hours. The mixture was diluted with water (300 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with 1N hydrochloric acid (2 x 50 mL), sodium bicarbonate solution (2 x 50 mL), dried (MgSO₄), and concentrated to give 27.3 g yellow oil.

¹H NMR (CDCl₃): δ 1.21 (t, 3H), 2.50 (s, 3H), 2.70 (t, 2H), 3.97 (t, 2H), 4.17 (q, 2H), 7.51 (d, 1H), 7.64 (s, 1H), 7.71 (d, 1H).

MS (APCI, pos.): 262, 216.

Step 2: Ethyl 3-[5-bromomethyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

The material from step 1 (27.3 g, 0.10 mol) was dissolved in carbon tetrachloride (50 mL), and *N*-bromosuccinimide (19.5 g, 0.11 mol) and AIBN (200 mg) was added. The mixture was refluxed for 5 hours, filtered by suction, and the filtrate was concentrated to give 35.4 g yellow oil.

¹H NMR (CDCl₃): δ 1.23 (t, 3H), 2.50 (s, 3H), 2.72 (t, 2H), 4.00 (t, 2H), 4.13 (q, 2H), 4.55 (s, 2H), 7.71 (d, 1H), 7.82 (d, 1H), 7.87 (s, 1H).

MS (APCI, pos.): 340, 342.

Step 3: Ethyl 3-[5-formyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

The crude material from step 2 was dissolved in DMSO (70 mL). Powdered K₂HPO₄ (18 g, 0.10 mol) and KH₂PO₄ (7 g, 0.05 mol) were added. The mixture was stirred at 80°C for 5 hours, diluted with water (500 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried (MgSO₄), and concentrated. After column chromatography (hexane, ethyl acetate 3:1) 4.8 g of the title compound was obtained.

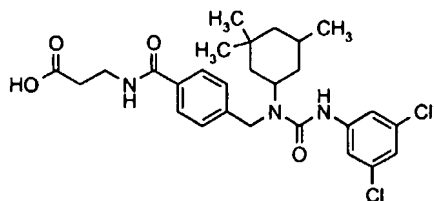
¹H NMR (CDCl₃): δ 1.23 (t, 3H), 2.75 (t, 2H), 4.04 (t, 2H), 4.13 (q, 2H), 8.03 (d, 1H), 8.26 (d, 1H), 8.35 (s, 1H), 10.17 (s, 1H).

MS (APCI, neg.): 275.

The following examples were prepared according to the general procedure (J).

EXAMPLE 176 (general procedure (J))

- 5 3-{4-[3-(3,5-Dichlorophenyl)-1-(3,3,5-trimethylcyclohexyl)ureidomethyl]benzoylamino}-propionic acid

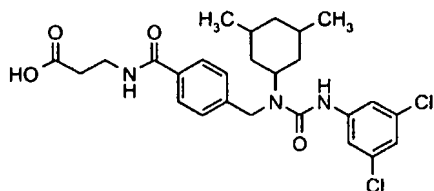


- ¹H NMR (DMSO-*d*₆): δ 1.14-1.29 (m, 5H), 1.33 - 1.37 (m, 1 H), 1.98 (brd, 1H), 2.49 (t, 2H),
10 3.44 (q, 2H), 4.50 (m, 1H), 4.65 (d, 2H), 7.11 (t, 1H), 7.29 (d, 2H), 7.57 (s, 2H), 7.78 (d, 2H),
8.85 (t, 1H), 8.62 (s, 1H), 12.21 (s, 1H).

MS (APCI, pos.): 536.2, 535.2, 534.2.

- 15 EXAMPLE 177 (general procedure (J))

3-{4-[3-(3,5-Dichlorophenyl)-1-(3,5-dimethylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

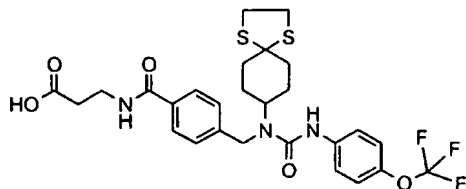


- 20 ¹H NMR (DMSO-*d*₆): δ 0.62 (q, 1H), 0.83 (d, 6H), 1.15 (m, 2H), 1.63 - 1.80 (m, 5H), 2.50 (t, 2H),
3.37 (m, 2H), 4.45 (s, 1H), 4.78 (s, 2H), 7.11 (s, 1H), 7.26 (d, 2H), 7.59 (s, 2H), 7.77 (d, 2H),
8.47 (t, 1H), 8.72 (s, 1H), 12.15 (brd, 1 H).

MS (APCI, pos.): 520.2

EXAMPLE 178 (general procedure (J))

3-{4-[1-(1,4-Dithiaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-
amino}propionic acid



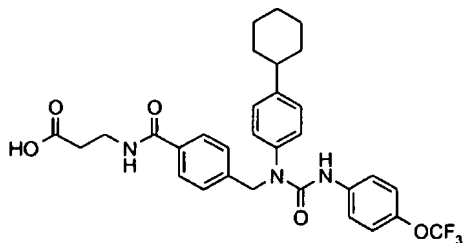
5

^1H NMR (DMSO- d_6): δ 1.62 (m, 4 H), 2.03 (m, 4 H), 3.24 (m, 4 H), 3.40 (m, 2 H), 4.13 (m, 1 H), 4.57 (s, 2 H), 7.23 (d, 2 H), 7.32 (d, 2 H), 7.54 (d, 2 H), 7.76 (d, 2 H), 8.46 (t, 1 H), 8.57 (s, 1 H), 12.20 (brd, 1 H).

10 MS (APCI, pos.): 598.2.

EXAMPLE 179 (general procedure (J))

3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-
propionic acid



15

^1H NMR (MeOH- d_4): δ 1.28 – 1.48 (m, 5H), 1.75 – 1.87 (m, 5H), 2.54 (m, 1H), 2.66 (t, 2H), 3.62 (t, 2H), 4.98 (s, 2H), 7.10 – 7.16 (m, 4H), 7.26 (d, 2H), 7.39 (d, 2H), 7.43 (d, 2H), 7.75 (d, 2H).

20

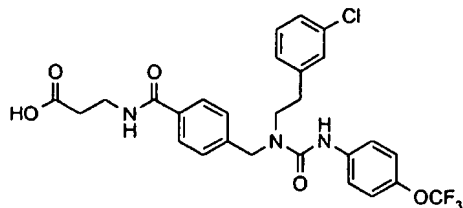
MS (APCI, pos): 584.2, 585.2, 586.2.

The following examples 180 to 229 were all found to displace more than 50% of the glucagon tracer when screened at 1 μM concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

25

EXAMPLE 180 (general procedure (J))

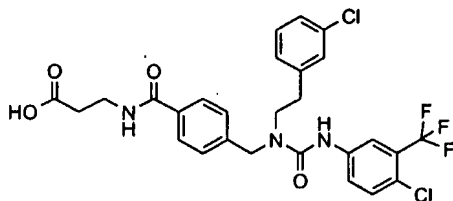
3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



5

EXAMPLE 181 (general procedure (J))

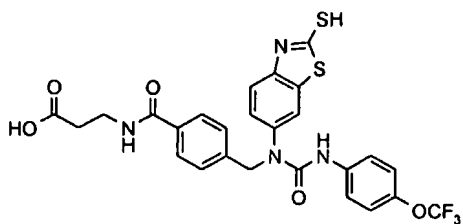
3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 182 (general procedure (J))

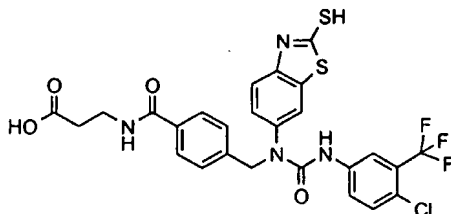
3-{4-[1-[2-(Mercaptobenzothiazol-6-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 183 (general procedure (J))

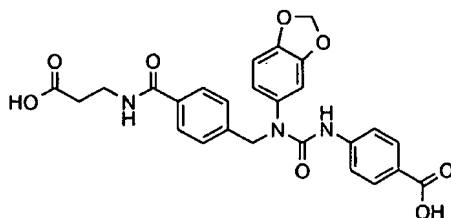
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-mercaptobenzothiazol-6-yl)ureidomethyl]-benzoylamino}propionic acid



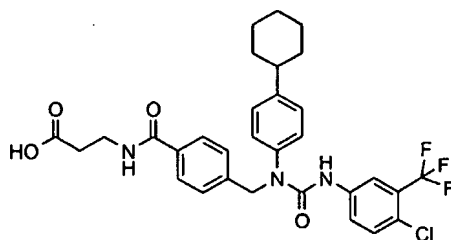
5

EXAMPLE 184 (general procedure (J))

4-{3-(Benzo[1,3]dioxo-5-yl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid

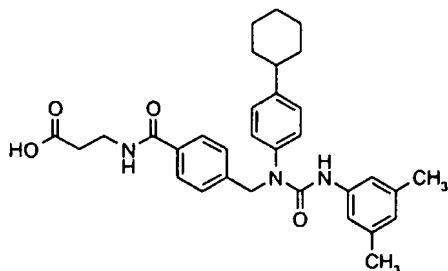
**10 EXAMPLE 185 (general procedure (J))**

3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}propionic acid



EXAMPLE 186 (general procedure (J))

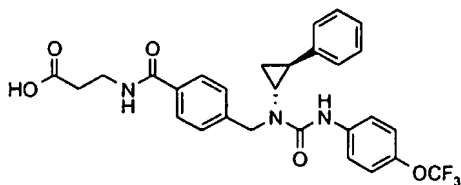
3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dimethylphenyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 187 (general procedure (J))

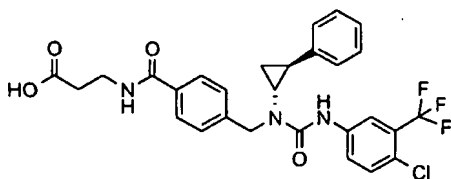
3-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



10

EXAMPLE 188 (general procedure (J))

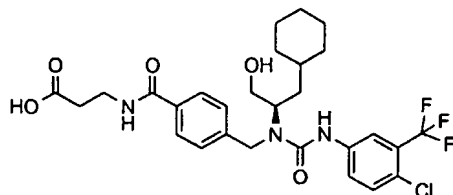
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-phenylcyclopropyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 189 (general procedure (J))

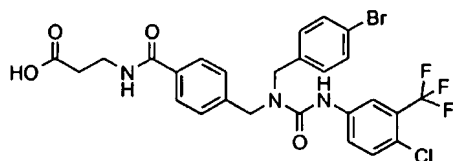
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-cyclohexyl-1-hydroxymethylethyl)ureido-methyl]benzoylamino}propionic acid



5

EXAMPLE 190 (general procedure (J))

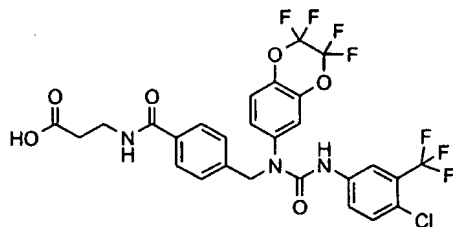
3-{4-[1-(4-Bromobenzyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid



10

EXAMPLE 191 (general procedure (J))

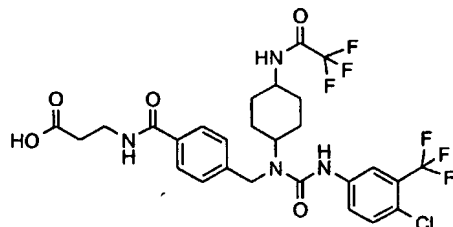
3-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-1-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]-dioxin-6-yl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 192 (general procedure (J))

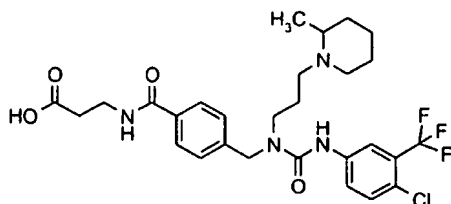
3-(4-{3-(4-Chloro-3-trifluoromethylphenyl)-1-[4-(2,2,2-trifluoroacetylaminocyclohexyl)ureido-methyl]benzoylamino}propionic acid



20

EXAMPLE 193 (general procedure (J))

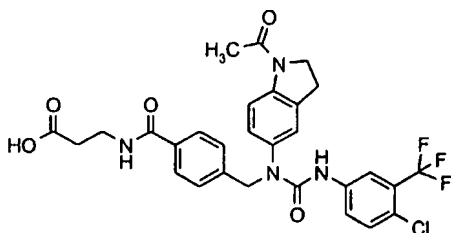
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(2-methylpiperidin-1-yl)propyl]ureidomethyl]-benzoylamino}propionic acid



5

EXAMPLE 194 (general procedure (J))

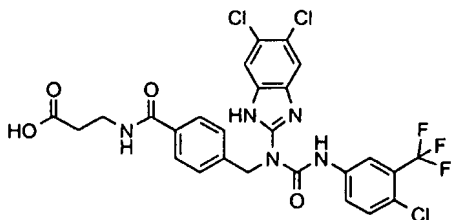
3-{4-[1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]-benzoylamino}propionic acid



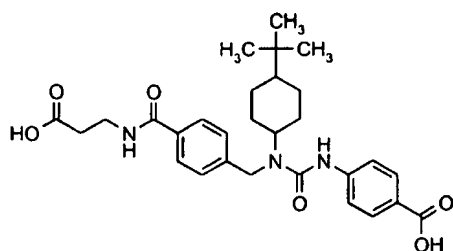
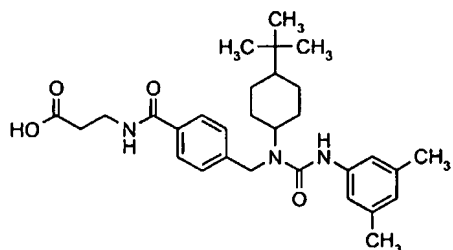
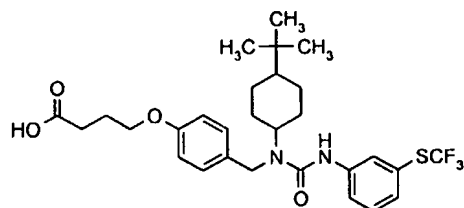
10

EXAMPLE 195 (general procedure (J))

3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(5,6-dichloro-1H-benzimidazol-2-yl)ureido-methyl]benzoylamino}propionic acid

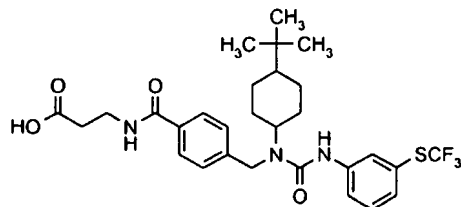


15

EXAMPLE 196 (general procedure (J))**4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid****5 EXAMPLE 197 (general procedure (J))****3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dimethylphenyl)ureidomethyl]benzoylamino}propionic acid****10 EXAMPLE 198 (general procedure (J))****4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]phenoxy}-butyric acid**

EXAMPLE 199 (general procedure (J))

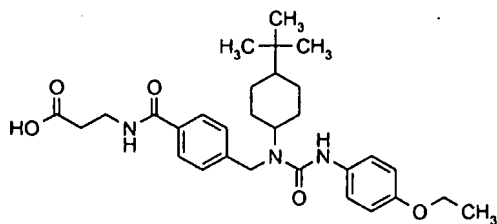
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-amino}propionic acid



5

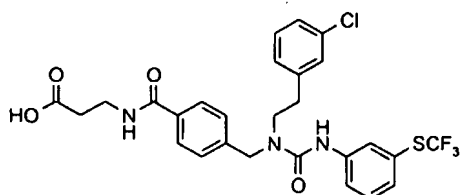
EXAMPLE 200 (general procedure (J))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-ethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



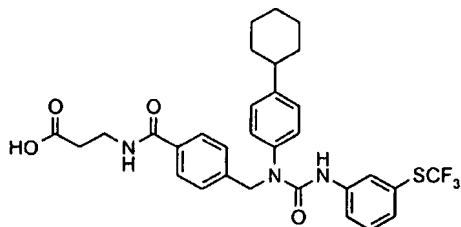
10 **EXAMPLE 201 (general procedure (J))**

3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-amino}propionic acid



EXAMPLE 202 (general procedure (J))

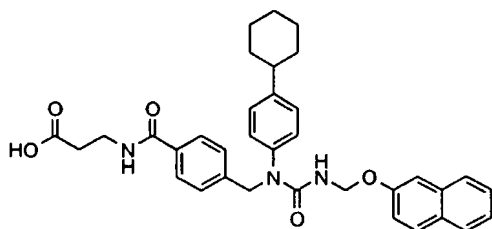
3-{4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}-propionic acid



5

EXAMPLE 203 (general procedure (J))

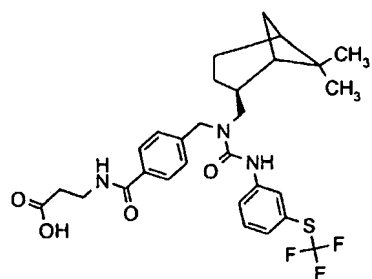
3-{4-[1-(4-Cyclohexylphenyl)-3-(naphthalen-2-yloxymethyl)ureidomethyl]benzoylamino}-propionic acid



10

EXAMPLE 204 (general procedure (J))

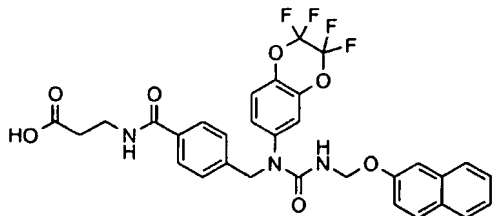
3-{4-[1-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylmethyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 205 (general procedure (J))

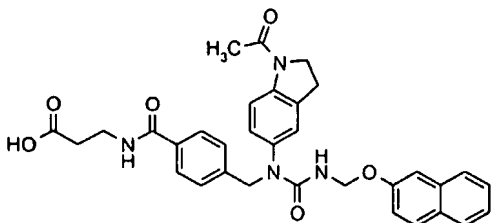
3-{4-[3-(Naphthalen-2-yloxymethyl)-1-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 206 (general procedure (J))

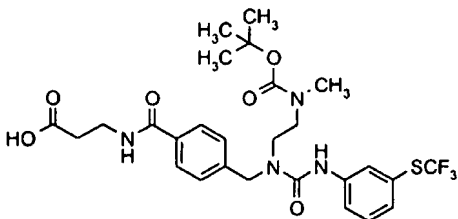
3-{4-[1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-(naphthalen-2-yloxymethyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 207 (general procedure (J))

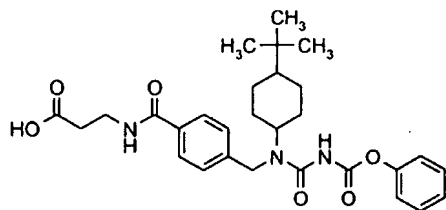
3-{4-[1-[2-(*N*-tert-Butoxycarbonyl-*N*-methylamino)ethyl]-3-(3-trifluoromethylsulfanylphenyl)-ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 208 (general procedure (J))

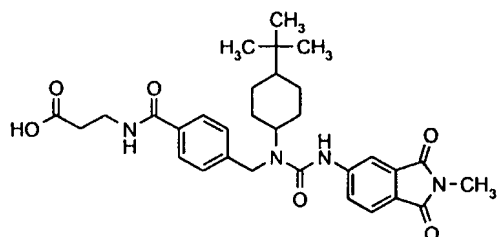
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(phoxycarbonyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 209 (general procedure (J))

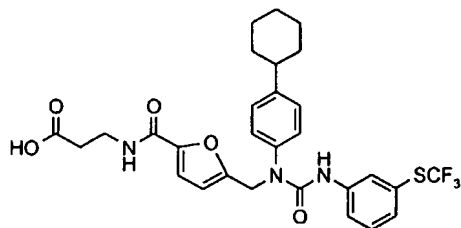
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 210 (general procedure (J))

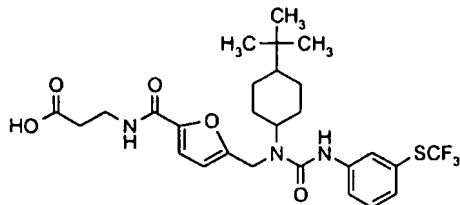
3-({5-[1-(4-cyclohexylphenyl)-3-(3-trifluoromethylsulfonylphenyl)ureidomethyl]furan-2-carbonyl}amino)propionic acid



15

EXAMPLE 211 (general procedure (J))

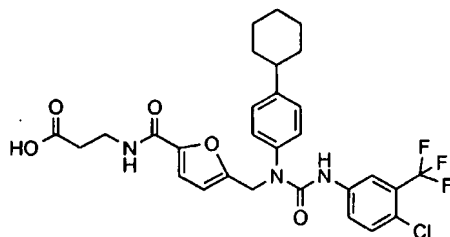
3-((5-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]furan-2-carbonyl)amino)propionic acid



5

EXAMPLE 212 (general procedure (J))

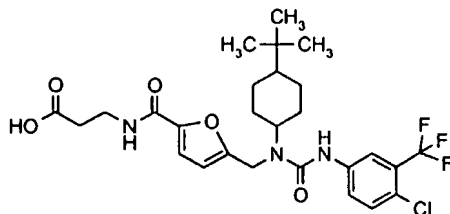
3-((5-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]furan-2-carbonyl)amino)propionic acid



10

EXAMPLE 213 (general procedure (J))

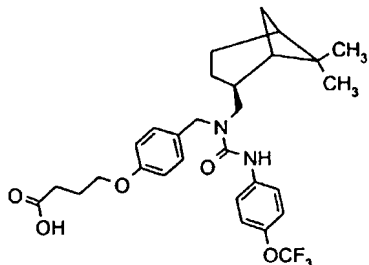
3-((5-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]furan-2-carbonyl)amino)propionic acid



15

EXAMPLE 214 (general procedure (J))

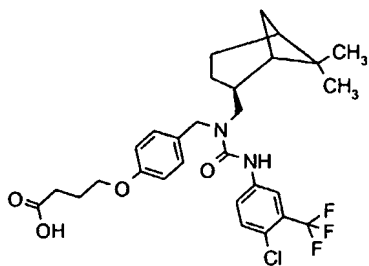
4-{4-[1-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylmethyl)-3-(4-trifluoromethoxyphenyl)ureido-methyl]phenoxy}butyric acid



5

EXAMPLE 215 (general procedure (J))

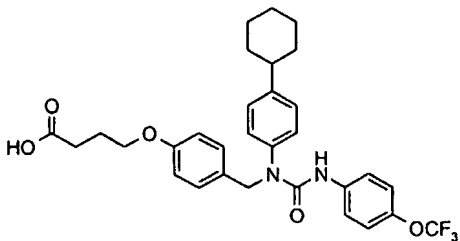
4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(6,6-dimethylbicyclo[3.1.1]hept-2-ylmethyl)-ureidomethyl]phenoxy}butyric acid



10

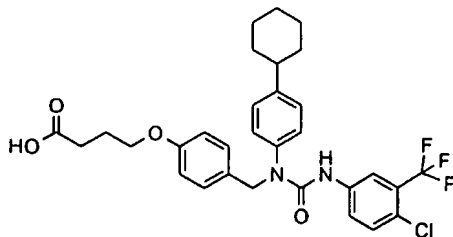
EXAMPLE 216 (general procedure (J))

4-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acid



EXAMPLE 217 (general procedure (J))

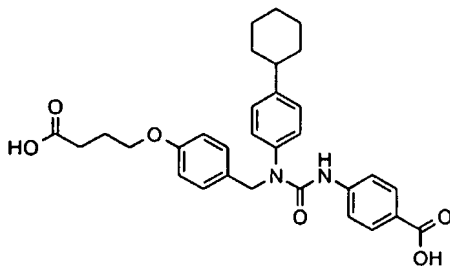
4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]phenoxy}-butyric acid



5

EXAMPLE 218 (general procedure (J))

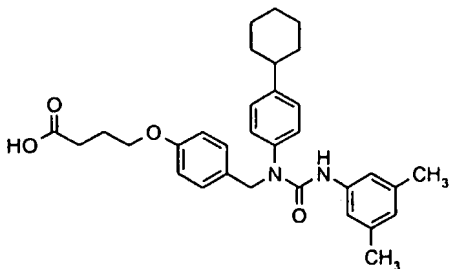
4-[3-[4-(3-Carboxypropoxy)benzyl]-3-(4-cyclohexylphenyl)ureido]benzoic acid

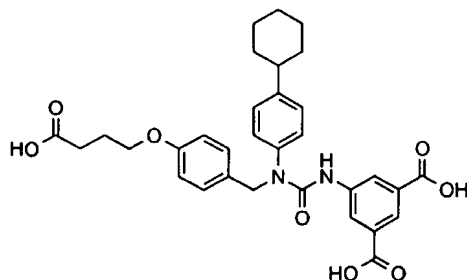
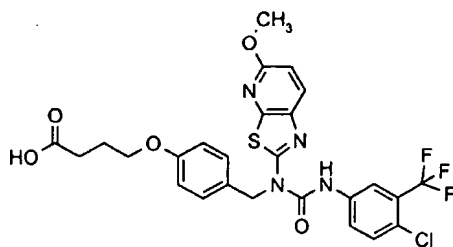
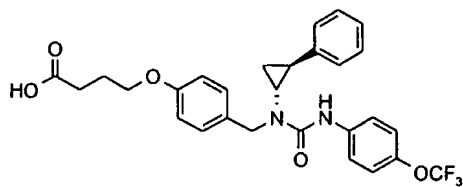
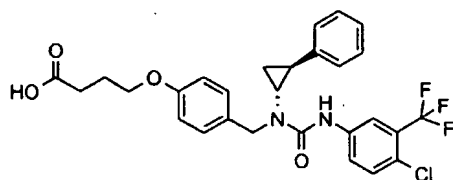


10

EXAMPLE 219 (general procedure (J))

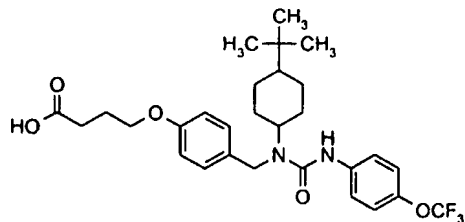
4-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dimethylphenyl)ureidomethyl]phenoxy}butyric acid



EXAMPLE 220 (general procedure (J))5-[3-[4-(3-Carboxypropoxy)benzyl]-3-(4-cyclohexylphenyl)ureido]isophthalic acid5 EXAMPLE 221 (general procedure (J))4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(5-methoxythiazolo[5,4-b]pyridin-2-yl)ureido-methyl]phenoxy}butyric acid10 EXAMPLE 222 (general procedure (J))4-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acidEXAMPLE 223 (general procedure (J))15 4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-phenylcyclopropyl)ureidomethyl]phenoxy}-butyric acid

EXAMPLE 224 (general procedure (J))

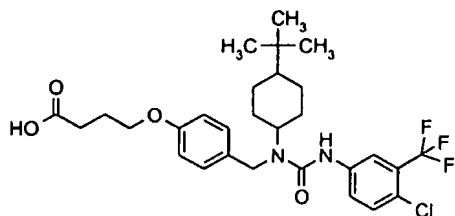
4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acid



5

EXAMPLE 225 (general procedure (J))

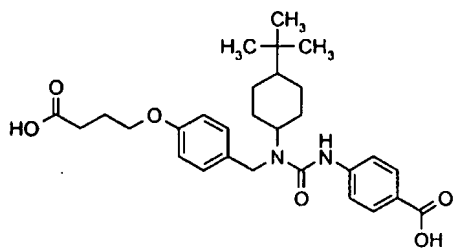
4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]phenoxy}-butyric acid



10

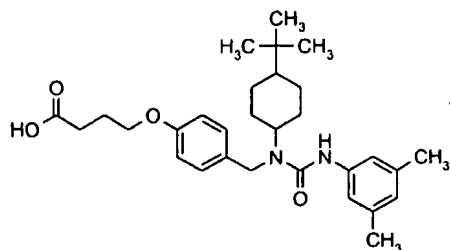
EXAMPLE 226 (general procedure (J))

4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(3-carboxypropoxy)benzyl]ureido}benzoic acid



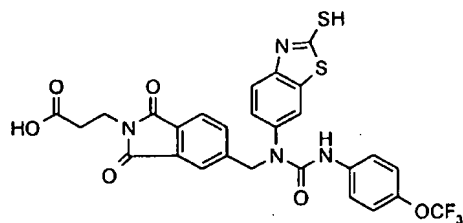
EXAMPLE 227 (general procedure (J))

4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dimethylphenyl)ureidomethyl]phenoxy}butyric acid



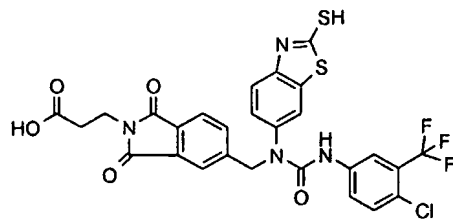
5 **EXAMPLE 228 (general procedure (J))**

3-{5-[1-(2-Mercaptobenzothiazol-6-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-1,3-dioxo-1,3-dihydro-isoindol-2-yl}propionic acid



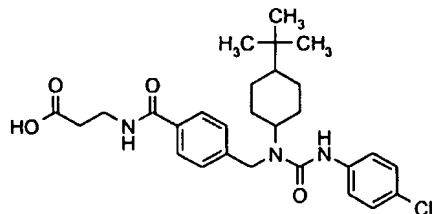
10 **EXAMPLE 229 (general procedure (J))**

3-{5-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-mercaptobenzothiazol-6-yl)ureidomethyl]1,3-dioxo-1,3-dihydro-isoindol-2-yl}propionic acid



15 **EXAMPLE 230 (General procedure (J))**

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoylamino}propionic acid

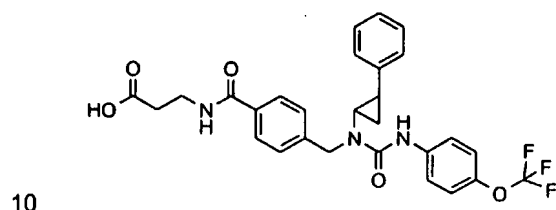


¹H NMR (DMSO-*d*₆): δ 0.80 (s, 9H), 0.94 (m, 1H), 1.11 (qt, 2H), 1.39 (qt, 2H), 1.69 (m, 4H), 2.45 (t, 2H), 3.44 (qt, 2H), 4.05 (m, 1H), 4.59 (s, 2H), 7.27 (d, 2H), 7.31 (d, 2H), 7.48 (d, 2H), 7.45 (d, 2H), 8.44 (t, 1H), 8.47 (s, 1H), 12.30 (brd s, 1H).

5 MS (APCI, pos): 516.2, 514.2, 361.2, 362.2, 289.2.

EXAMPLE 231 (general procedure (J))

3-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



¹H NMR (DMSO-*d*₆): δ 1.36 – 1.50 (m, 2H), 2.36 (m, 1H), 2.45 (t, 2H), 2.79 (quintet, 1H), 3.43 (qt, 2H), 4.54 (d, 1H), 4.75 (d, 1H), 7.06 (d, 2H), 7.16 (t, 1H), 7.23 – 7.30 (m, 6H), 7.58 (d, 2H), 7.74 (d, 2H), 8.46 (s, 1H), 8.48 (t, 1H), 12.20 (brd s, 1H).

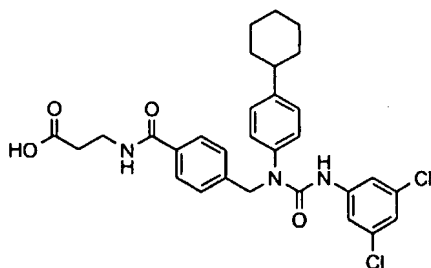
15

MS (APCI, pos): 542.2, 543.2, 544.2, 339.1.

EXAMPLE 232 (general procedure (J))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid

20



¹H NMR (DMSO-*d*₆): δ 1.10 – 1.42 (m, 5H), 1.60 – 1.80 (m, 5H), 2.45 (t, 2H), 3.43 (qt, 2H), 4.92 (s, 2H), 7.12 – 7.20 (M, 5H), 7.30 (d, 2H), 7.58 (s, 2H), 7.74 (d, 2H), 8.46 (t, 1H), 8.55 (s, 1H).

25

MS (APCI, pos): 568.2, 569.2, 570.2, 571.2.

Alternative method for the preparation of the compound:

To a solution of 4-formylbenzoic acid (27.4 g, 0.18 mol) in DMF (300 mL) was added *N*-ethyl-
5 *N*'-3-dimethylaminopropylcarbodiimide (34.5 g, 0.18 mol) and *N*-hydroxybenzotriazole (29.9 g, 0.22 mol). The resulting mixture was stirred at room temperature for 1 hour, then β -alanine ethyl ester hydrochloride (65.4 g, 0.42 mol) and diisopropylethylamine (76 mL, 0.44 mol) was added. After 16 hours stirring at ambient temperature the reaction mixture was partitioned between water (600 mL) and ethyl acetate (600 mL). The organic phase was washed suc-
10 cessively with hydrochloric acid (1N, 300 mL), saturated aqueous ammonium chloride (300 mL), water (2 x 300 mL) and brine (300 mL). The solvent was removed by rotary evaporation to leave an oil, which crystallised upon standing to afford 29.0 g (65%) of 3-(4-formylbenzoylamino)propionic acid ethyl ester.

15 ¹H NMR (DMSO-*d*₆): δ 1.18 (t, 3H); 2.62 (t, 2H); 3.54 (q, 2H); 4.09 (q, 2H); 8.00 (s, 4H); 8.78 (t, 1H); 10.08 (s, 1H).

To a well stirred solution of 3-(4-formylbenzoylamino)propionic acid ethyl ester (13.8 g, 55.3 mmol) in ethanol (150 mL) was added a solution of 4-cyclohexylaniline (9.70 g, 55.3 mmol) in
20 ethanol (75 mL). The mixture was heated to reflux for 30 minutes, and then acetic acid (50 mL) and sodium cyanoborohydride (3.50 g, 55.5 mmol) were added. After 10 minutes of additional heating, the mixture was cooled on an ice-bath. The solid precipitate was collected by filtration, washed several times with cold water and dried in a vacuum oven overnight to afford 18.16 g (80%) of 3-{4-[(4-cyclohexylphenylamino)methyl]benzoylamino}propionic acid
25 ethyl ester.

¹H NMR (CDCl₃): δ 1.28 (t, 3H); 1.35 (m, 5H); 1.78 (m, 5H); 2.38 (m, 1H); 2.64 (t, 2H); 3.74 (q, 2H); 4.18 (q, 2H); 4.36 (s, 2H); 6.53 (d, 2H); 6.81 (bt, 1H); 7.00 (d, 2H); 7.43 (d, 2H); 7.72 (d, 2H).

30

3-{4-[(4-Cyclohexylphenylamino)methyl]benzoylamino}propionic acid ethyl ester (15.0 g, 0.37 mol) was dissolved in dichloromethane (250 mL), and 3,5-dichlorophenylisocyanate (6.9 g, 0.37 mol) was added. The mixture was stirred overnight at room temperature. The solvent was removed by rotary evaporation, and the crystalline residue was re-dissolved in ethanol
35 (400 mL). Sodium hydroxide (100 mL, 4N) was added, and the reaction mixture was left at

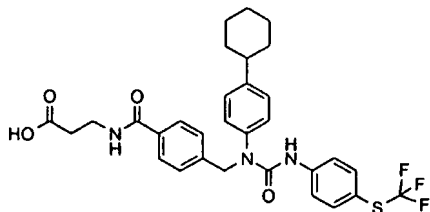
room temperature for 30 min. Water (600 mL) was added and the mixture was cooled on an ice bath. The clear solution was then acidified with hydrochloric acid (100 mL, 4N), and the resulting precipitate subsequently collected by filtration. Recrystallisation from acetonitrile / water afforded 15.5 g of the title compound as a white powder.

5

^1H NMR ($\text{DMSO}-d_6$): δ 1.36 (m, 5H); 1.78 (m, 6H); 2.50 (t, 2H); 3.44 (q, 2H); 4.92 (s, 2H); 7.12 (d, 1H); 7.16 (d, 2H); 7.21 (d, 2H); 7.32 (d, 2H); 7.60 (d, 2H); 7.75 (d, 2H); 8.45 (t, 1H); 8.53 (s, 1H); 12.20 (bs, 1H).

10 EXAMPLE 233 (general procedure (J))

3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfanylphenyl)-ureidomethyl]benzoylamino}-propionic acid



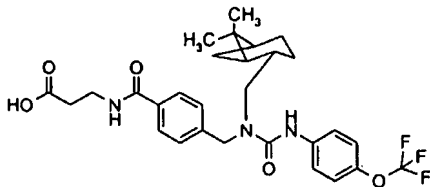
15 ^1H NMR ($\text{DMSO}-d_6$): δ 1.10 – 1.35 (m, 5H), 1.50 – 1.75 (m, 5H), 2.40 (m, 1H), 2.47 (t, 2H), 3.45 (t, 2H), 4.81 (s, 2H), 6.98 (d, 2H), 7.10 (d, 2H), 7.21 (d, 2H), 7.33 (d, 2H), 7.36 (d, 2H), 7.57 (d, 2H).

MS (APCI, pos): 600.2, 601.2, 602.2.

20

EXAMPLE 234 (general procedure (J))

3-{4-[1-([(1S,2R,5R)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



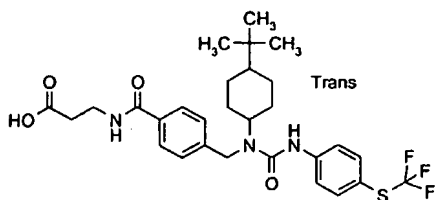
25

^1H NMR ($\text{MeOH}-d_4$): δ 0.90 (d, 1H), 1.05 (s, 3H), 1.15 (s, 3H), 1.49 (m, 1H), 1.80 - 1.95 (m, 5H), 2.36 - 2.47 (m, 2H), 2.62 (t, 2H), 3.40 (d, 2H), 3.61 (t, 2H), 4.70 (qt, 2H), 7.16 (d, 2H), 7.35 (d, 2H), 7.41 (d, 2H), 7.78 (d, 2H).

5 MS (APCI, pos): 562.2, 563.1.

EXAMPLE 235 (general procedure (J))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-(trifluoromethoxysulfonylphenyl)ureidomethyl)-benzoylamino}propionic acid



10

^1H NMR (CDCl_3): δ 0.80 (s, 9H), 0.90 (d, 1H), 1.20 (qt, 2H), 1.40 (qt, 2H), 1.90 (t, 4H), 2.75 (t, 2H), 3.70 (qt, 2H), 4.10 (brd t, 1H), 4.50 (s, 2H), 6.50 (s, 1H), 6.90 (t, 1H), 7.20 (d, 2H), 7.40 (d, 2H), 7.50 (d, 2H), 7.70 (d, 2H).

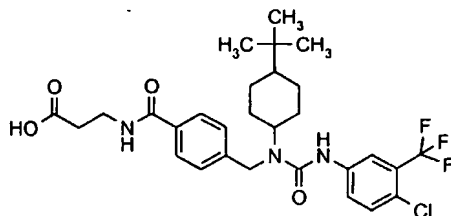
15

MS (APCI, pos): 580.2, 581.2.

EXAMPLE 236 (general procedure (J))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoyl-amino}propionic acid

20

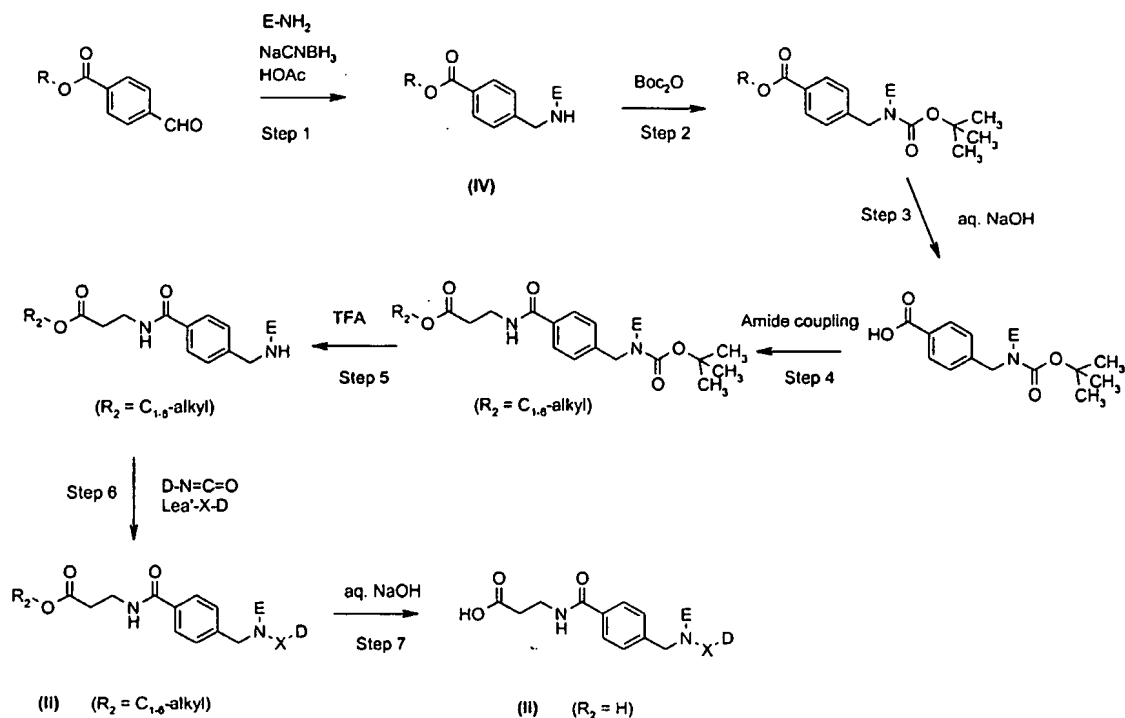


25

^1H NMR ($\text{DMSO}-d_6$): δ 0.78 (s, 9H), 1.10 (m, 1H), 1.33 (m, 2H), 1.50 (m, 4H), 1.75 (m, 2H), 2.40 (t, 2H), 3.43 (qt, 2H), 4.24 (quintet, 1H), 4.69 (s, 2H), 7.27 (d, 2H), 7.53 (d, 1H), 7.74 - 7.79 (m, 3H), 8.03 (s, 1H), 8.45 (t, 1H), 8.85 (s, 1H); 12.00 (brd s, 1H).

MS (APCI, pos): 582.2, 361.2.

General procedure (K) for the solution phase synthesis of compounds of the general formula (II):



5

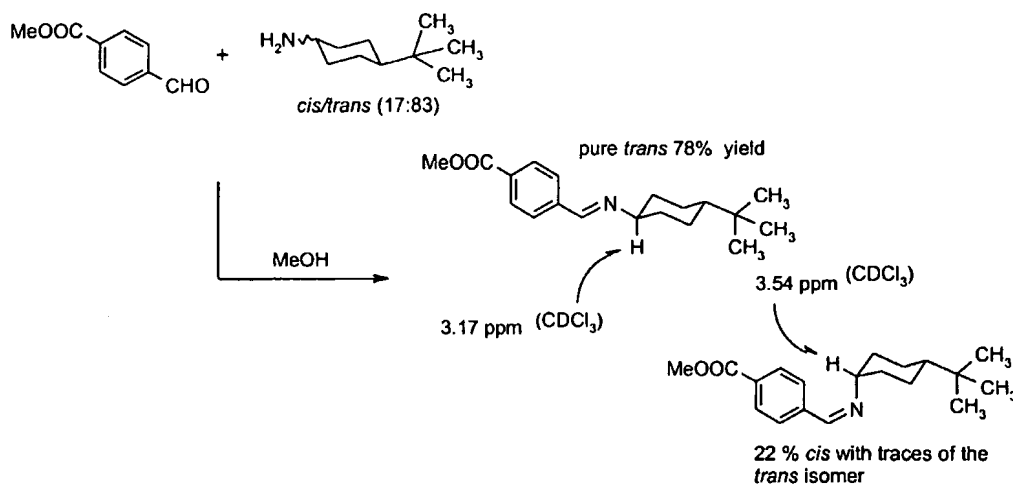
wherein R is C₁₋₆-alkyl,

V, X, D, and E are as defined in general formula (I), and

10 Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these can either be performed by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

15

Step 1: *trans*-4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester

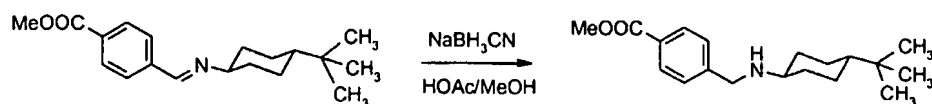
- 5 4-Formylbenzoic acid methyl ester (10.6 g, 64.4 mmol) was dissolved in methanol (200 mL). A 17:83 *cis/trans* mixture of 4-*tert*-butylcyclohexylamine (10.0 g, 64.4 mmol, Aldrich) was added, leading to immediate precipitation of white crystals. The mixture was heated to reflux for 30 min to complete imine formation, then cooled to 0°C on an ice bath. The crystalline pure *trans*-4-[(4-*tert*-butylcyclohexylimino)methyl]benzoic acid methyl ester was then collected by filtration, and dried overnight in vacuo. Yield: 15.3 g (78%).

^1H NMR (CDCl_3), 300 MHz: δ 8.37 ppm. (s, 1H); 8.06 (d, 2H); 7.77 (d, 2H); 3.92 (s, 3H); 3.17 (m, 1H); 1.83 (m, 4H); 1.60 (m, 2H), 1.09 (m, 3H); 0.87 (s, 9H).

- 15 Micro Analysis: Calculated for $\text{C}_{19}\text{H}_{27}\text{NO}_2$
 C: 75.71%, H: 9.03%, N: 4.65%. Found:
 C: 75.60%, H: 9.37%, N: 4.68%.

- The mother liquid was taken to dryness to leave 4.2 g (22%) white solid, which according to NMR consisted mainly of the imino *cis* isomer.

^1H NMR (CDCl_3), 300 MHz: δ 8.36 ppm. (s, 1H); 8.07 (d, 2H); 7.81 (d, 2H); 3.92 (s, 3H); 3.54 (m, 1H); 1.55 - 1.92 (m, 8H); 1.14 (m, 1H); 0.90 (s, 9H).



trans-4-[(4-*tert*-Butylcyclohexylimino)methyl]benzoic acid methyl ester (21.0 g, 69.2 mmol) was suspended in methanol (300 mL), and acetic acid (50 mL) was added. To the resulting clear solution was added sodium cyanoborohydride (3.5 g, 55.5 mmol), and the mixture was stirred at ambient temperature for 30 min. The reaction volume was then reduced to one third by rotary evaporation, and ethyl acetate (500 mL) was added. The organic phase was washed with sodium carbonate solution (5%, 500 mL), and dried with Na_2SO_4 . The solvent was removed by rotary evaporation to leave the title material as a white crystalline solid sufficiently pure for further reactions. Yield: 21.1 g (100%).

^1H NMR (CDCl_3), 300 MHz: δ 7.98 ppm. (d, 2H); 7.38 (d, 2H); 3.90 (s, 3H); 3.86 (s, 2H); 2.39 (m, 1H); 2.01 (m, 2H); 1.77 (m, 2H); 1.51 (bs, 1H); 0.93-1.18 (m, 5H); 0.82 (s, 9H).

HPLC-MS (Method B: $R_t = 4.87$ m/z = 304 ($M + 1$)).

Alternatively, step 1 can be performed in the same way as step A of the general procedure (F).

Step 2: *trans*-4-[(*N*-(*tert*-Butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino)methyl]benzoic acid methyl ester

trans-4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (20.0 g, 65.9 mmol) was dissolved in THF (300 mL). Di-*tert*-butylpyrocarbonate (16.0 g, 73.4 mmol) and diisopropylethylamine (12.0 g, 92.9 mmol) was added and the clear solution stirred overnight at ambient temperature. Solvent was removed by rotary evaporation.

Step 3: *trans*-4-[(*N*-(*tert*-Butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino)methyl]benzoic acid

The crystalline residue from step 2 was re-dissolved in ethanol (200 mL) and aqueous sodium hydroxide solution (100 mL, 4N) was added whereafter the mixture was heated to 70°C for 4 hours. After cooling, the reaction volume was reduced to one third by rotary evaporation, and water (300 mL) was added. The mixture was extracted with diethyl ether (2 x 200 mL) to remove traces of non-hydrolysed material. The aqueous phase was then acidified to pH 3.0 by addition of aqueous 4N HCl, whereupon the title material separated out of solution

as compact crystals. The crystals were washed once with water and dried overnight in a vacuum oven (40°C). Yield: 24.3 g (93%).

¹H NMR (CDCl₃), 300 MHz: δ 8.04 ppm. (d, 2H); 7.31 (d, 2H); 4.39 (bs, 2H); 4.05 (bs, 1H);
5 1.78 (bd, 4H); 0.95-1.65 (m, 14 H); 0.83 (s, 9H). The signals were broad due to the presence of *cis/trans* carbamate isomers.

Micro analysis Calculated for C₂₃H₃₅NO₄:

C, 70.92%; H, 9.06%; N, 3.60%. Found:

10 C, 70.67%; H, 9.36%; N: 3.57%.

Step 4: Methyl *trans*-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]-benzoylaminopropanoate

Trans-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]benzoic acid (22.0
15 g, 56.5 mmol) and 1-hydroxybenzotriazole (8.6 g, 57.0 mmol, containing 12% w/w water) was dissolved in DMF (300 mL). *N*-Dimethylaminopropyl-*N'*-ethylcarbodiimide hydrochloride (10.9 g, 56.8 mmol), β-alanine methyl ester (8.4 g, 60 mmol) and diisopropylethylamine (25 mL, 142 mmol) were added and the clear solution stirred at 20°C for 16 hours. Solvent was removed by rotary evaporation and the residual oil re-dissolved in ethyl acetate (500 mL).
20 The organic phase was washed with 5% aqueous sodium hydrogen carbonate solution (2 x 500 mL), 0.5 M citric acid (2 x 250 mL) and brine before being dried with anhydrous Na₂SO₄. Solvent was removed and the residual oil evaporated twice from acetonitrile. The oil was used without further purification. Yield: 24.0 g (89%).

25 ¹H NMR (CDCl₃), 300 MHz: δ 7.69 (d, 2H); 7.28 (d, 2H); 6.81 (t, 1H); 4.38 (bs, 2H); 3.23 (s, 3H); 3.21 (t, 2H); 2.66 (t, 2H); 1.75 (bd, 4H); 0.95-1.65 (m, 14 H); 0.80 (s, 9H).

Step 5: Methyl *trans*-4-[[*N*-(4-*tert*-butylcyclohexyl)aminomethyl]benzoylaminopropanoate tri-fluoroacetate

30 Methyl *trans*-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]benzoylaminopropanoate (19.5 g, 41.1 mmol) was dissolved in a mixture of TFA (200 mL) and dichloromethane (200 mL), while cooling on an ice bath. The ice bath was removed and the mixture allowed to stir at room temperature for 30 min. Solvent was removed by rotary evaporation, and the crystalline residue recrystallized from ethyl acetate/heptane. Yield: 14.8
35 g (74%).

^1H NMR (CDCl_3), 300 MHz: δ 9.98 (trace of TFA); 8.06 (bs, 2H); 7.73 (d, 2H); 7.41 (d, 2H); 7.34 (t, 1H); 4.21 (t, 2H); 3.75 (s, 3H); 3.74 (t, 2H); 3.04 (m, 1H); 2.70 (t, 2H); 2.17 (bd, 2H); 1.95 (bd, 2H); 1.50 (m, 2H); 0.92-1.15 (m, 3H); 0.85 (s, 9H).

5

Micro analysis. Calculated for $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_3 \cdot \text{C}_2\text{HF}_3\text{O}_2$:

C, 59.00%; H, 7.22%; N, 5.73%. Found:

C, 58.95%; H, 7.37%; N: 5.70%.

10 General procedure for forming isocyanates from (substituted) anilines and diphosgene to be used in step 6:

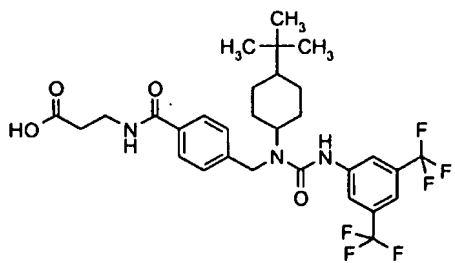
To a solution of the amine in anhydrous toluene was added 1N HCl in diethyl ether (5 eq). A precipitate formed. The toluene was evaporated. To the solid was added more anhydrous toluene and the toluene was evaporated again to remove excess HCl. This procedure was repeated 2-3 times. To a mixture of the solid in toluene (about 10 g in 300 mL) was added diphosgene (trichloromethyl chloroformate) (10 eq or more) or phosgene. The mixture was refluxed under nitrogen overnight. A clear solution was obtained. If more solid was present, more diphosgene was added and reflux continued. When a clear solution was obtained, the reaction was concentrated in vacuo at 60-90°C to remove the toluene and excess diphosgene until the theoretical weight was obtained. To the crude isocyanate was added more anhydrous toluene and concentrated again to remove excess HCl. The crude isocyanate was used without further purification.

25

This method gives the isocyanates in pure form, which may be used in step 6.

EXAMPLE 237 (general procedure (K))

3-{4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]benzoyl-amino}propionic acid



Trans

30

Step 6, using a phenyl carbamate or nitrophenyl carbamate

3,5-Bis-(trifluoromethyl)aniline (2.0 g, 8.7 mmol) was dissolved in dichloromethane (80 mL) and *N,N*-diisopropylethylamine (1.6 mL, 9.6 mmol) was added followed by slow addition of phenyl chloroformate (1.1 mL, 8.7 mmol). The resulting mixture was stirred at room temperature for 16 hours. The mixture was successively washed with 1N hydrochloric acid (3 x 100 mL), water (3 x 100 mL), a mixture of water and saturated aqueous sodium hydrogen carbonate (1:1, 2 x 100 mL) and a mixture of water and saturated aqueous sodium chloride (1:1, 3 x 100 mL), dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from heptane containing a little diethyl ether to afford 1.3 g (43%) of (3,5-bis-trifluoromethyl-phenyl)carbamic acid phenyl ester as a solid.

Calculated for C₁₅H₉F₆NO₂:

C, 51.59%; H, 2.60%; N, 4.01%. Found:

C, 51.27%; H, 2.56%; N, 4.01%;

C, 51.40%; H, 2.57%; N, 3.92%.

The above carbamic acid phenyl ester (1.0 g, 2.9 mmol) was mixed with 3-{4-[(4-*tert*-butyl-cyclohexylamino)methyl]benzoylamino}propionic acid methyl ester, trifluoroacetate (1.07 g, 2.9 mmol), prepared as described above and triethylamine (1.2 mL, 8.6 mmol) in dichloromethane (55 mL) and the resulting mixture was refluxed for 4 hours. The cooled reaction mixture was diluted with toluene (50 mL) and washed with water (3 x 50 mL) and a mixture of water and saturated aqueous sodium chloride (1:1, 3 x 100 mL), dried (MgSO₄) and concentrated in vacuo to afford 1.2 g (67%) of 3-{4-[3-(3,5-bis-trifluoromethylphenyl)-1-(4-*tert*-butyl-cyclohexyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

¹H NMR (CDCl₃): δ 0.83 (9H, s), 0.9-1.5 (5H, m), 1.88 (4H, bt), 7.62 (H, t), 3.72 (5H, m), 4.18 (1H, bt), 4.57 (2H, s), 6.80 (1H, s), 6.90 (1H, t), 7.38 (2H, d), 7.46 (1H, s), 7.77 (2H, d), 7.80 (2H, s).

HPLC-MS (Method B): R_t = 9.07 min, m/z = 630 (M + 1).

Step 7:

The above propionic acid methyl ester (1.0 g, 1.6 mmol) was dissolved in warm ethanol (50 mL), and after cooling to room temperature 4N aqueous sodium hydroxide (6 mL) was added. The reaction mixture was stirred at room temperature for 1 hour. Glacial acetic acid

(10 mL) was added and the mixture was concentrated in vacuo. The residue was partitioned between water (50 mL) and ethyl acetate (2 x 50 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 0.88 g (93%) of the title compound as a solid.

5

¹H NMR (DMSO-*d*₆): δ 0.83 (9H, s), 0.9-1.5 (5H, m), 1.70 (4H, bt), 2.50 (2H, t, below DMSO), 3.45 (2H, q, below water), 4.05 (1H, bt), 4.62 (2H, s), 7.32 (2H, d), 7.60 (2H, d), 8.24 (2H, s), 8.45 (1H, t), 9.00 (1H, s), 12 (1H, bs).

10 HPLC-MS (Method B): R_t = 8.60 min, m/z = 616 (M + 1).

Calculated for C₃₀H₃₅F₆N₃O₄ x 0.25H₂O:

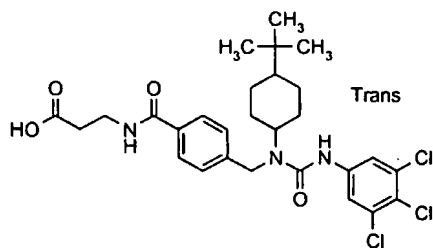
C, 57.47%; H, 5.57%; N, 6.93%. Found:

C, 57.60%; H, 5.81%; N, 6.47%;

15 C, 57.63%; H, 5.76%; N, 6.45%.

EXAMPLE 238 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,4,5-trichlorophenyl)ureidomethyl]benzoylamino}-propionic acid



20

Step 6, using isocyanate formed in situ from (substituted) anilines and triphosgene:

Triphosgene (bis-trichloromethylcarbonate) (152 mg, 0.51 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0°C. To this solution a solution of 3,4,5-trichloroaniline (303 mg, 1.54 mmol) and diisopropylethylamine (540 μL, 3.1 mmol) in dichloromethane (3 mL) was added at 0°C over 1 hour. The mixture was then allowed to reach room temperature. To this mixture a solution of methyl *trans*-4-[(4-*tert*-butylcyclohexyl)aminomethyl]benzoylamino-propanoate trifluoroacetate (576 mg, 1.54 mmol) and diisopropylethylamine (800 μL) in dichloromethane (10 mL) was added and stirring at room temperature was continued for 30 minutes. The mixture was diluted with more dichloromethane (10 mL) and washed with satu-

30

rated aqueous citric acid (2 x 20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to afford 653 mg (71%) of 3-{4-[1-(4-*trans-tert*-butylcyclohexyl)-3-(3,4,5-trichlorophenyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

- 5 ^1H NMR ($\text{DMSO}-d_6$): δ 0.81 (s, 9H), 0.92 (m, 1H), 1.12 (m, 2H), 1.44 (m, 2H), 1.68 (m, 4H), 2.56 (t, 2H), 3.45 (q, 2H), 3.59 (s, 3H), 4.05 (b t, 1H), 4.58 (s, 2H), 7.30 (d, 2H), 7.78 (d, 2H), 7.83 (s, 2H), 8.44 (t, 1H), 8.75 (s, 1H).

Step 7:

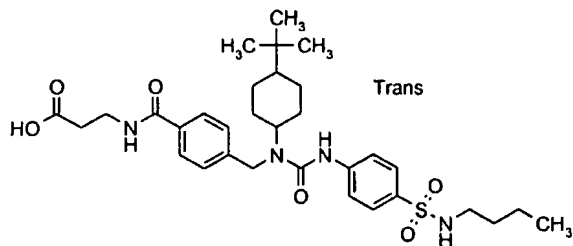
- 10 Hydrolysis of this ester using the method described in example 92, step D afforded the title compound (495 mg, 78%).

- ^1H NMR ($\text{DMSO}-d_6$): δ 0.82 (s, 9H), 0.91 (m, 1H), 1.10 (m, 2H), 1.39 (m, 2H), 1.71 (m, 4H), 2.51 (t, 2H), 3.35 (q, 2H), 4.01 (t, 1H), 4.59 (s, 2H), 7.30 (d, 2H), 7.78 (d, 2H), 7.85 (s, 2H),
15 8.46 (t, 1H), 8.76 (s, 1H), 12.21 (b s, 1H).

EXAMPLE 239 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-butylsulfamoylphenyl)ureidomethyl]benzoylamino}-propionic acid

20



- 4-Nitrophenylsulfonyl chloride (3.0 g, 13.5 mmol) was dissolved in THF and a catalytic amount of 4-dimethylaminopyridine and 1-butylamine (4.0 mL, 41 mmol) was added and the mixture was refluxed for 16 hours. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL) and a 10% aqueous solution of sodium hydrogen carbonate (50 mL). The organic phase was dried (MgSO_4) and concentrated in vacuo to afford 3.01 g (86%) of *N*-butyl-4-nitrobenzenesulfonamide as a solid.

30

¹H NMR (CDCl₃): δ 0.89 (3H, t), 1.30 (2H, m), 1.48 (2H, m), 3.03 (2H, t), 4.9 (1H, b), 8.06 (2H, d), 8.37 (2H, d).

Sodium dithionite (11.4 g, 65 mmol) and sodium carbonate (5.6 g, 53 mmol) were dissolved
5 in water (65 mL) and heated to 70°C. A suspension of the above 4-nitrophenylsulfonamide
(2.64 g, 10.2 mmol) in methanol (65 mL) was added and the resulting mixture was stirred at
70°C for 1.5 hour. The cooled mixture was filtered and the volume of the filtrate was reduced
by 50% in vacuo. The aqueous mixture was extracted with ethyl acetate (3 x 60 mL), and the
combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford 0.14 g
10 (6%) of 4-amino-*N*-butylbenzenesulfonamide as a solid.

¹H NMR (DMSO-*d*₆): δ 0.80 (3H, t), 1.2-1.4 (4H, m), 2.65 (2H, q), 5.90 (2H, s), 6.60 (2H, d),
7.04 (1H, t), 7.40 (2H, d).

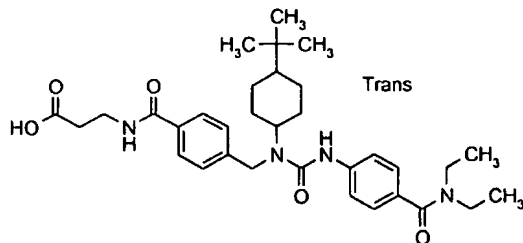
15 HPLC-MS (Method B): R_t = 5.15 min, m/z = 229 (M + 1).

The above 4-aminophenylsulfonamide (0.14 g) was dissolved in dichloromethane (6 mL),
N,N-diisopropylethylamine (172 μL, 1 mmol) and phenyl chloroformate (122 μL, 0.92 mmol)
and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture
20 was diluted with dichloromethane (50 mL) and was washed with 1N hydrochloric acid (3 x 20
mL), water (3 x 20 mL), a mixture of water and a saturated solution of sodium hydrogen car-
bonate (1:1, 2 x 20 mL) and a mixture of water and a saturated solution of sodium chloride
(1:1, 2 x 20 mL). Drying (MgSO₄) and concentration in vacuo afforded crude (4-butyl-
sulfamoylphenyl)carbamic acid phenyl ester.

25

From the above crude carbamic acid phenyl ester and 3-{4-[(4-*trans-tert*-butylcyclohexyl-
amino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate the title compound
was obtained similarly as described above.

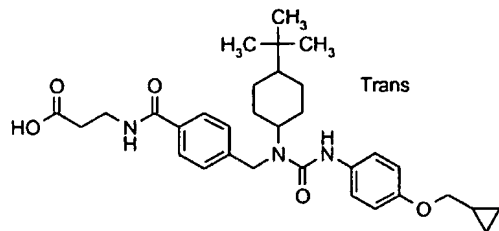
30 HPLC-MS (Method B): R_t = 7.37 min, m/z = 615 (M + 1).

EXAMPLE 240 (general procedure (K))3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-diethylcarbamoylphenyl)ureidomethyl]benzoylamino}propionic acid

5

The title compound was prepared similarly as described above starting from 4-nitrobenzoyl chloride, diethylamine and 3-{4-[(4-*trans*-*tert*-butylcyclohexylamino)methyl]benzoylamino}-propionic acid methyl ester trifluoroacetate.

10 HPLC-MS (Method B): $R_t = 6.76$ min, $m/z = 579$ ($M + 1$).

EXAMPLE 241 (general procedure (K))3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

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4-Nitrophenol (2.0 g, 14.4 mmol) was dissolved in DMF (50 mL) and potassium carbonate (6.0 g, 43 mmol) and bromomethylcyclopropane (1.51 mL, 16 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous solution of sodium chloride (2 x 50 mL). Drying ($MgSO_4$) and concentration afforded 2.23 g (75%) of 1-cyclopropylmethoxy-4-nitrobenzene as an oil.

25 1H NMR ($CDCl_3$): δ 0.40 (2H, m), 0.58 (2H, m), 1.30 (1H, m), 3.89 (2H, d), 6.94 (2H, d), 8.12 (2H, d).

The above 4-nitrobenzene (2.0 g, 9.5 mmol) was dissolved in ethanol (50 mL) and tin(II) chloride dihydrate (10.7 g, 48 mmol) was added and the mixture was refluxed for 24 hours. After cooling, the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (40 mL) and 1N aqueous sodium hydroxide (180 mL). This mixture was filtered through
5 celite. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford 0.88 g (52%) of 4-cyclopropylmethoxyaniline.

¹H NMR (DMSO-*d*₆): δ 0.25 (2H, m), 0.53 (2H, m), 1.15 (1H, m), 3.63 (2H, d), 4.55 (2H, s),
10 6.4-6.5 (3H, m), 6.62 (2H, d).

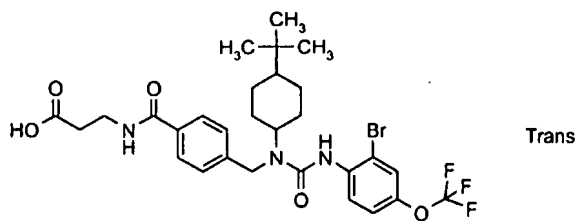
From the above aniline and 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}-propionic acid methyl ester trifluoroacetate the title compound was prepared similarly as described in example 238.

15 ¹H NMR (DMSO-*d*₆): δ 0.42 (2H, m), 0.62 (2H, m), 0.85 (9H, s), 0.92 (1H, m), 1.1-1.4 (5H, m), 1.9 (4H, bt), 2.70 (4H, m), 4.14 (1H, t), 4.52 (2H, s), 6.08 (1H, s), 6.77 (2H, d), 6.88 (1H, t), 7.10 (2H, d), 7.40 (2H, d), 7.76 (2H, d).

20 HPLC-MS (Method B): R_t = 7.73 min, m/z = 550 (M + 1).

EXAMPLE 242 (general procedure (K))

3-{4-[3-(2-Bromo-4-trifluoromethoxyphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}propionic acid



4-Trifluoromethoxyaniline (1.0 g, 5.6 mmol) was dissolved in glacial acetic acid (10 mL). Bromine (585 μL, 11 mmol) dissolved in glacial acetic acid (2 mL) was added with stirring during 10 minutes at room temperature. The resulting mixture was stirred at room temperature for 2 hours and then poured into water (100 mL). The solid formed (2,5-dibromo-4-trifluoromethoxyaniline) was filtered off. The filtrate was made alkaline with solid sodium hy-
30

dioxide and extracted with dichloromethane (100 mL), dried (MgSO₄) and concentrated (30°C; 200 mBar) to afford 0.57 g (40%) of 2-bromo-4-trifluoromethoxyaniline.

¹H NMR (DMSO-*d*₆): δ 5.55 (2H, bs), 6.85 (1H, d), 7.10 (1H, dd), 7.37 (1H, d).

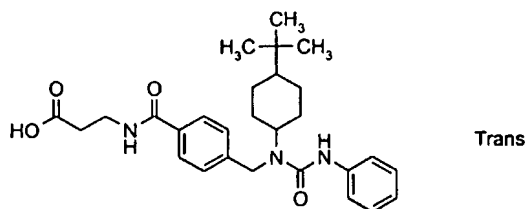
5

From the above 2-bromoaniline and 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate the title compound was prepared similarly as described in example 238.

10 ¹H NMR (DMSO-*d*₆): δ 0.86 (9H, s), 0.95 (1H, m), 1.2 (2H, m), 1.4 (2H, m), 1.9 (4H, m), 2.74 (2H, t), 3.75 (2H, q), 4.16 (1H, t), 4.60 (2H, s), 6.85 (1H, t), 6.88 (1H, s), 7.16 (1H, dd), 7.31 (1H, d), 7.43 (2H, d), 7.76 (2H, d), 8.26 (2H, d).

EXAMPLE 243 (general procedure (K))

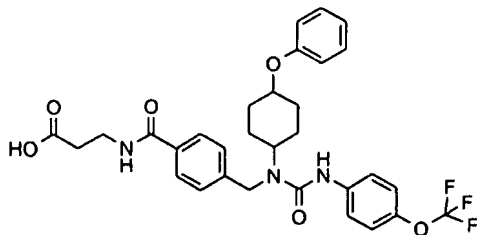
15 3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-phenylureidomethyl]benzoylamino}propionic acid



20 From 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate and phenylisocyanate the title compound was prepared similarly as described in the alternative method for preparing example 92 according to the general procedure (K).

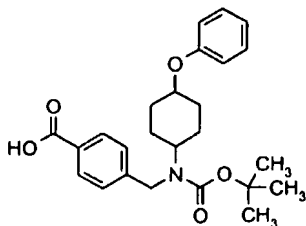
25 ¹H NMR (DMSO-*d*₆): δ 0.84 (9H, s), 0.93 (1H, m), 1.2 (2H, m), 1.4 (2H, m), 1.85 (4H, m), 2.63 (2H, t), 3.70 (2H, q), 4.19 (1H, t), 4.58 (2H, s), 6.75 (1H, s), 6.97 (1H, t), 7.2-7.3 (4H, m), 7.4 (3H, m), 7.80 (2H, d).

HPLC-MS (Method B): R_t = 7.28 min, m/z = 480 (M + 1).

EXAMPLE 244 (general procedure (K))**3-{4-[1-(4-Phenoxycyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid**

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Synthesis of intermediate 4-[[*tert*-butoxycarbonyl-(4-phenoxycyclohexyl)amino]methyl]-benzoic acid:



- 10 Methyl 4-(bromomethyl)benzoate (5.0 g, 22 mmol) was dissolved in DMF (50 mL) and *trans*-4-aminocyclohexanol (3.04 g, 26 mmol) was added followed by addition of potassium carbonate (6.08 g, 44 mmol). The reaction mixture was heated to 80°C for 16 hours. The reaction mixture was diluted with ethyl acetate (300 mL) and water (200 mL) was added. The aqueous phase was extracted with ethyl acetate (100 mL), and the combined organic phases
- 15 were washed with water (2 x 100 mL) and dried (MgSO₄). The organic phase was concentrated *in vacuo* to give 2.5 g of *trans*-4-[(4-hydroxycyclohexylamino)methyl]benzoic acid methyl ester.

HPLC-MS (method B): m/z: 264, R_t = 3.48 min.

20

- trans*-4-[(4-Hydroxycyclohexylamino)methyl]benzoic acid methyl ester (2.46 g, 9.3 mmol) was suspended in sodium hydroxide (1N, 9 mL). Di-*tert*-butylpyrocarbonate (2.44 g, 11.2 mmol) dissolved in THF (11 mL) was added during 15 minutes. Additional THF (8 mL) was added and the reaction mixture was stirred for 16 hours. The reaction mixture was evaporated *in vacuo* until THF was removed. Water (25 mL), sodium hydroxide (1N, 1.5 mL), and
- 25 diethyl ether (50 mL) was added. The water phase was extracted with diethyl ether (25 mL)

and the combined organic phases were washed with an aqueous solution of sodium hydrogensulphate (10%, 30 mL), water (3 x 20 mL), and dried (MgSO₄). The organic phase was concentrated in vacuo to give 3.60 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-hydroxycyclohexyl)-amino]methyl]benzoic acid methyl ester.

5

HPLC-MS (method B): m/z: 364, R_t = 5.75 min.

trans-4-[[*tert*-Butoxycarbonyl-(4-hydroxycyclohexyl)amino]methyl]benzoic acid methyl ester (1.0 g, 2.75 mmol) was dissolved in THF (4 mL) and triphenylphosphine (1.12 g, 4.1 mmol) was added followed by addition of phenol (0.26 g, 2.75 mmol). Diethylazodicarboxylate (0.72 g, 4.1 mmol) dissolved in THF (2 mL) was added drop wise, and the reaction mixture was stirred for 16 hours. The reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (100g silica) using ethyl acetate and heptane (1:9) as eluent to give 0.27 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-phenoxy-cyclohexyl)amino]methyl]benzoic acid methyl ester. The ester was dissolved in ethanol (5 mL) and sodium hydroxide (4N, 1 mL) was added. After 5 hours the reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (25 mL), and hydrochloric acid (4N, 1.3 mL) was added. The organic phase was washed with water (3 x 10 mL), dried (MgSO₄) and concentrated in vacuo to give 0.25 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-phenoxy-cyclohexyl)amino]methyl]benzoic acid.

10
15
20

¹H NMR (DMSO-*d*₆): δ 12.85 (1H, broad), 7.90 (2H, d), 7.36 (2H, d), 7.22 (2H, t), 6.88 (3H, m), 4.53 (1H, m), 4.43 (2H, m), 2.0-1.2 (18H, m).

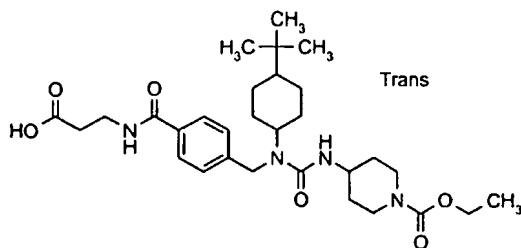
25 This intermediate was used for the synthesis the title compound.

¹H NMR (DMSO-*d*₆): δ 12.2 (1H, broad), 8.58 (2H, s), 8.48 (1H, t), 7.79 (2H, s), 7.55 (2H, s), 7.37 (2H, s), 7.25 (4H, m), 6.91 (3H, m), 4.67 (2H, s), 4.58 (1H, s), 4.24 (1H, m), 3.42 (2H, dd), 2.52-2.48 (2H, m), 2.00-1.90 (2H, m), 1.80-1.55 (4H, m), 1.50-1.40 (2H, m).

30

EXAMPLE 245 (general procedure (K))

4-{3-(*trans*-4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}piperidine-1-carboxylic acid ethyl ester

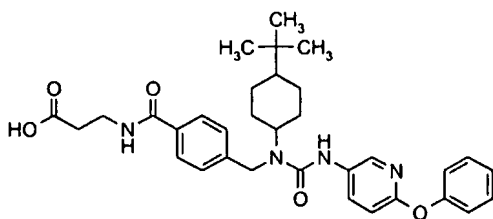


5

^1H NMR (DMSO- d_6): δ 12.2 (1H, broad), 8.42 (1H, t), 7.72 (2H, d), 7.25 (2H, d), 6.02 (1H, d), 4.42 (2H, broad), 4.02 (2H, q), 3.92-3.60 (3H, m), 3.50-3.40 (2H, m), 2.90-2.70 (2H, m), 1.80-0.80 (10H, m), 0.80 (13H, s).

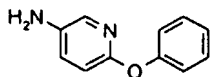
EXAMPLE 246 (general procedure (K))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(6-phenoxy pyridin-3-yl)ureidomethyl]benzoylamino}-propionic acid



15 HPLC-MS (method B): m/z : 573, R_t = 7.23 min.

Synthesis of intermediate 5-amino-2-phenoxy pyridine:



20 Phenol (0.9 g, 9.5 mmol) was dissolved in sodium hydroxide (50% solution, 12 mL). 5-Nitro-2-chloropyridine (1.5 g, 9.5 mmol) in toluene (15 mL) was added followed by addition of tetrabutylammonium bromide (0.3 g, 0.95 mmol). The reaction mixture was stirred for 16 hours at 20°C and 5 hours at 80°C where after it was cooled to room temperature and diethyl ether (100 mL) added. The organic phase was washed with water (5 x 50 mL), dried (MgSO₄), and

25 concentrated in vacuo to give 1.0 g of 5-nitro-2-phenoxy pyridine.

M.p. 85-87°C.

5-Nitro-2-phenoxy pyridine (0.5 g, 2.3 mmol) was added portion wise to a solution of stannous chloride (2.6 g, 12 mmol) dissolved in concentrated hydrochloric acid (10 mL) at a temperature of 0-5°C. The reaction mixture was then stirred at 20°C for 16 hours. Sodium carbonate (5 g) and aqueous ammonia (50 mL) was added. The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with water (2 x 40 mL), dried (MgSO₄), and concentrated in vacuo to give 0.3 g of 5-amino-2-phenoxy pyridine.

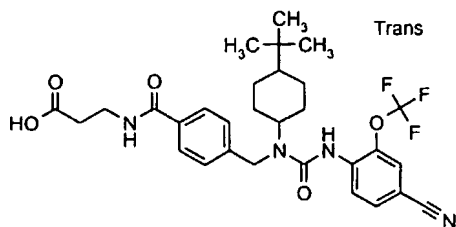
¹H NMR (DMSO-*d*₆): δ 7.55 (1H, s), 7.33 (2H, dd), 7.08 (2H, dd), 6.93 (2H, d), 6.75 (1H, d), 5.12 (2H, broad).

This compound was transformed into the corresponding phenylcarbamate (as described for in example 237 and used in the synthesis of the title compound).

¹H NMR (DMSO-*d*₆): δ 8.51 (1H, s), 8.45 (1H, broad), 8.20 (1H, d), 7.90 (1H, dd), 7.75 (2H, d), 7.35 (4H, m), 7.15 (1H, t), 7.05 (2H, d), 6.92 (1H, d), 4.57 (2H, broad), 4.02 (1H, broad), 3.40 (m), 3.38 (2H, m), 1.80-0.80 (10H, m), 0.80 (13H, s).

EXAMPLE 247 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyano-2-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

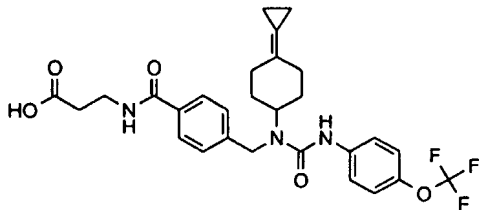


¹H NMR (DMSO-*d*₆): δ 12.2 (1H, broad), 8.48 (1H, t), 8.32 (1H, broad), 7.92 (1H, s), 7.90 (1H, d), 7.75 (3H, m), 7.34 (2H, d), 4.60 (2H, broad), 4.03 (1H, m), 3.45 (2H, m), 1.80-0.85 (9H, m), 0.80 (9H, s).

HPLC-MS (method B): m/z: 589, R_t = 8.07 min.

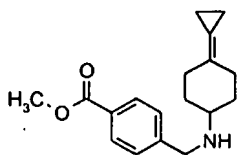
EXAMPLE 248 (general procedure (K))

3-{4-[1-(4-Cyclopropylidenecyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



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Synthesis of intermediate 4-[(4-cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester:



- 10 Cyclopropyltriphenylphosphonium bromide (10.8 g, 28 mmol) was suspended in dry THF (30 mL) and cooled to -60°C. *N*-Butyllithium (1.6M in THF, 17 mL, 27 mmol) was added dropwise at -40 to -60°C. The temperature was raised to 20°C and after 3 hours at this temperature, the reaction mixture was cooled to -60°C. 1,4-Cyclohexane dione mono ethylene ketal (4.0 g, 26 mmol) dissolved in THF (30 mL) was added at -60°C whereafter the temperature was
- 15 raised to 20°C. After 16 hours the reaction mixture was diluted with THF (75 mL) filtered through hyflo and concentrated in vacuo. The residue was purified by flash chromatography (4 x 15 cm column of silica) using heptane and ethyl acetate (4:1) as eluent to give 2.5 g of 8-cyclopropylidene-1,4-dioxo-spiro[4.5]decane (cf Synthetic Communications 21(20), 2015-2023, 1991).

20

- Silica gel 60 (6.0 g) was suspended in dichloromethane (12 mL) and oxalic acid (10% in water, 0.6 g) was added. After 20 minutes 8-cyclopropylidene-1,4-dioxo-spiro[4.5]decane (1.6 g, 8.9 mmol) dissolved in dichloromethane (5 mL) was added and the reaction mixture was stirred for 48 hours at 20°C. Sodium hydrogen carbonate (200 mg) was added and after 1
- 25 hour the reaction mixture was filtered. The filtrate was concentrated in vacuo and the crude product of 4-cyclopropylidenecyclohexanone was used for the next step without further purification.

4-Aminomethylbenzoic acid methyl ester, hydrochloride salt (2.2 g, 11 mmol) was suspended in 1,2 dichloropropane (30 mL) and an aqueous saturated solution of potassium carbonate (15 mL) was added. The next day the organic phase was isolated and dried (MgSO₄). 4-Cyclopropylidenecyclohexanone (1.5 g, 11 mmol) dissolved in dichloromethane (15 mL) was added followed by addition of acetic acid (400 µL) and sodium triacetoxyborohydride (3.3 g, 16.5 mmol). After 72 hours at 20°C the reaction mixture was diluted with dichloromethane (50 mL) and washed with aqueous saturated sodium hydrogen carbonate (2 x 30 mL) and water (5 x 30 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (50 g silica) using ethyl acetate and methanol (97:3) as eluent to give 1.1 g of 4-[(4-cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester.

¹H NMR (DMSO-*d*₆): δ 7.90 (2H, d), 7.48 (2H, d), 3.84 (3H, s), 3.80 (2H), 3.63 (1H, m), 2.60-0.90 (12H, m).

HPLC-MS (method B): m/z: 286, R_t = 4.45 min.

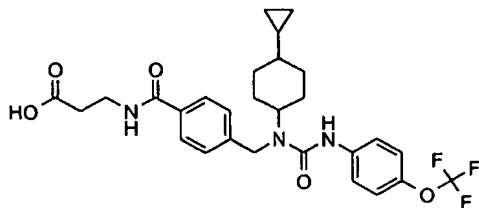
This intermediate product was used for the synthesis of the title compound.

¹H NMR (DMSO-*d*₆): δ 2.2 (1H, broad), 8.60 (1H, s), 8.43 (1H, t), 7.75 (2H, d), 7.55 (2H, d), 7.30 (2H, d), 7.22 (2H, d), 4.65 (2H, broad), 4.32 (1H, m), 3.45 (2H, m), 2.60-0.90 (14H, m).

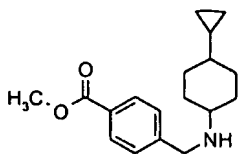
HPLC-MS (method B): m/z: 546, R_t = 7.38 min.

EXAMPLE 249 (general procedure (K))

3-{4-[1-(4-Cyclopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



Synthesis of intermediate 4-[(4-cyclopropylcyclohexylamino)methyl]benzoic acid methyl ester:



4-[(4-Cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester (1.1 g, 3.9 mmol) was dissolved in DMF (40 mL) and p-toluenesulfonic acid hydrazide (2.8 g, 15.4 mmol) was added. The reaction was heated to 100°C for 16 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (75 mL) and water (40 mL) was added. The aqueous phase was extracted with ethyl acetate (25 mL) and the combined organic phases washed with aqueous saturated sodium hydrogen carbonate (2 x 30 mL) and water (5 x 30 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (25 g silica) using heptane and ethyl acetate (1:1) as eluent to give 4-[(4-cyclopropylcyclohexylamino)methyl]benzoic acid methyl ester.

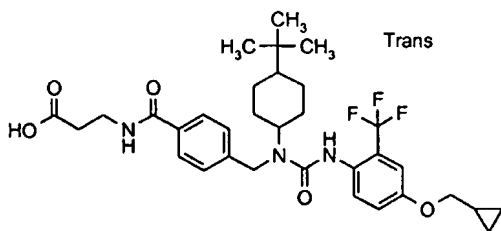
This intermediate product was used for the synthesis of the title compound.

¹H NMR (DMSO-*d*₆): δ 12.2 (1H, broad), 8.51 (1H, s), 8.43 (1H, t), 7.75 (2H, dd), 7.55 (2H, d), 7.32 (2H, dd), 7.22 (2H, d), 4.68 (1H, s), 4.60 (1H, s), 4.10 (1H, m), 3.45 (2H, dd), 1.80-0.25 (13H, m).

HPLC-MS (method B): m/z: 548, R_t = 7.38 min.

EXAMPLE 250 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxy-2-trifluoromethylphenyl)ureido-methyl]benzoylamino}propionic acid



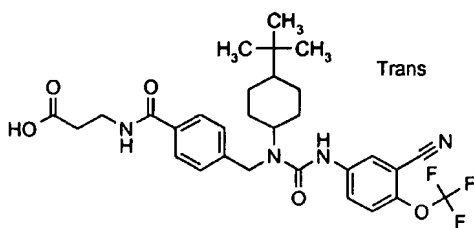
The intermediate, 4-cyclopropylmethoxy-2-trifluoromethylaniline, was prepared analogously to the aniline intermediate used in example 241.

^1H NMR ($\text{DMSO}-d_6$): δ 12.1 (1H, broad), 8.45 (1H, t), 7.98 (1H, broad), 7.75 (2H, d), 7.32 (2H, d), 7.29 (1H, s), 7.15 (2H, m), 4.52 (2H, broad), 3.88 (2H, d), 3.45 (1H, m), 1.80-0.85 (10H, m), 0.80 (9H, s), 0.60 (2H, m), 0.33 (2H, m).

5 HPLC-MS (method B): m/z : 618, R_t = 6.65 min.

EXAMPLE 251 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3-cyano-4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid



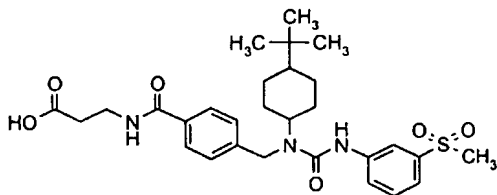
10

^1H NMR ($\text{DMSO}-d_6$): δ 12.2 (s, broad), 8.90 (1H, s), 8.43 (1H, t), 8.10 (1H, s), 7.90 (2H, dd), 7.75 (2H, d), 7.55 (1H, d), 7.32 (2H, d), 4.61 (2H, broad), 4.04 (2H, m), 3.45 (2H, m), 1.80-0.85 (10H, m), 0.80 (9H, s).

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EXAMPLE 252 (general procedure (K))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfonylphenyl)ureidomethyl]benzoylamino}-propionic acid



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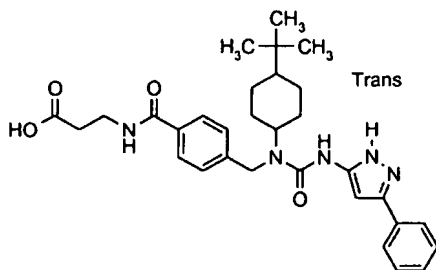
The title compound was prepared from the corresponding 3-methylsulfonyl compound (general procedure (K)) followed by oxidation of the sulfonyl group and hydrolysis of the propionic acid ester.

25 ^1H NMR ($\text{DMSO}-d_6$): δ 12.2 (s, broad), 8.76 (1H, s), 8.45 (1H, t), 8.07 (1H, s), 7.83 (1H, d), 7.74 (2H, d), 7.50 (2H, m), 7.30 (2H, d), 4.60 (2H, broad), 4.08 (2H, d), 3.45 (2H, t), 3.18 (3H, s), 2.50 (2H, t), 1.80-0.85 (9H, m), 0.80 (9H, s).

HPLC-MS (method B): m/z : 558, R_t = 6.52 min.

EXAMPLE 253 (general procedure (K))

- 5 3-{4-[1-(4-*trans-tert*-Butylcyclohexyl)-3-(5-phenyl-2*H*-pyrazol-3-yl)ureidomethyl]-benzoylamino}propionic acid



Using isocyanate formed in situ from 5-amino-3-phenylpyrazole and triphosgene:

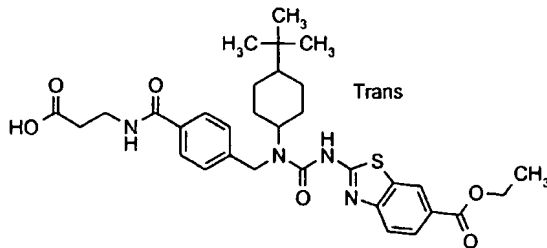
- 10 To a suspension of 5-amino-3-phenylpyrazole (183 mg, 8.7 mmol) in 1,2-dichloroethane (5 mL) was added *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol) followed by addition of triphosgene (115 mg, 0.38 mmol). The solution was heated to reflux for two hours. To this mixture a solution of 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate (350 mg, 0.70 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol) in DMF (4 mL) was added and stirring at 80°C was continued for 2 hours. The mixture was allowed to cool to room temperature, poured into water (50 mL) and the water phase was washed ethyl acetate (2 x 50 mL). The combined organic phases were concentrated in vacuo and purification on silica column with dichloromethane/methanol (95:5) afforded the 3-{4-[1-(4-*trans-tert*-butylcyclohexyl)-3-(5-phenyl-2*H*-pyrazol-3-yl)ureidomethyl]-benzoylamino}propionic acid methyl ester as a solid which was redissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 30 min. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration. Recrystallisation from acetonitrile afforded the title compound.

25

¹H NMR (CDCl₃): δ 0.82 (9H, s), 0.9-1.5 (5H, m), 1.69 (4H, bt), 4.09 (1H, bt), 4.58 (2H, s), 6.64 (1H, s), 7.25-7.50 (5 H, m), 7.60-7.80 (4H, m), 8.50 (1H, t), 9.0 (1H, s).

HPLC-MS (Method B): R_t = 6.52 min, m/z = 546 (M+1).

30

EXAMPLE 254 (general procedure (K))**2-{3-(4-*trans*-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}-benzothiazole-6-carboxylic acid ethyl ester**

5

Using isocyanate formed in situ from (substituted) 2-aminobenzothiazole and diphosgene in pyridine:

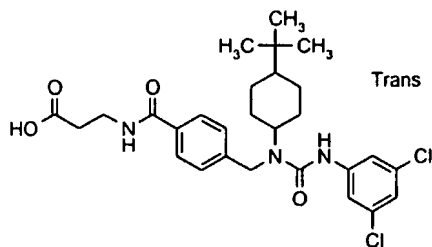
Ethyl-2-aminobenzothiazole-6-carboxylate (262 mg, 1.2 mmol) was suspended in pyridine (4 ml). Diphosgene (80 μ L, 0.66 mmol) was added and the solution was stirred for two hours at room temperature. To this mixture a solution of 3-{4-[(4-*trans*-*tert*-butylcyclohexylamino)-methyl]benzoylamino}propionic acid methyl ester trifluoroacetate (300 mg, 0.61 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.4 mmol) in DMF (4 mL) was added and stirring at 80°C was continued for 2 hours. The mixture was allowed to cool to room temperature and poured into acetonitrile (50 mL), the resulting precipitate was filtered off and the filtrate was then partitioned between ethyl acetate (50 mL) and hydrochloric acid (2 x 50 mL, 1 N). The organic phase was concentrated in vacuo to give an oil which was redissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 30 min. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration to afford the title compound.

20

HPLC-MS (Method B): R_t = 7.65 min, m/z = 609 (M^+).

EXAMPLE 255 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid



5

¹H NMR (DMSO-*d*₆): δ 12.2 (s, 1H), 8.68 (s, 1H), 8.45 (t, 1H), 7.74 (d, 2H), 7.61 (s, 2H), 7.30 (d, 2H), 7.11 (s, 1H), 4.57 (s, 2H), 4.02 (m, 1H), 3.43 (m, 2H), 2.50 (m, 2H), 1.8-0.75 (m, 9H), 0.80 (s, 9H)

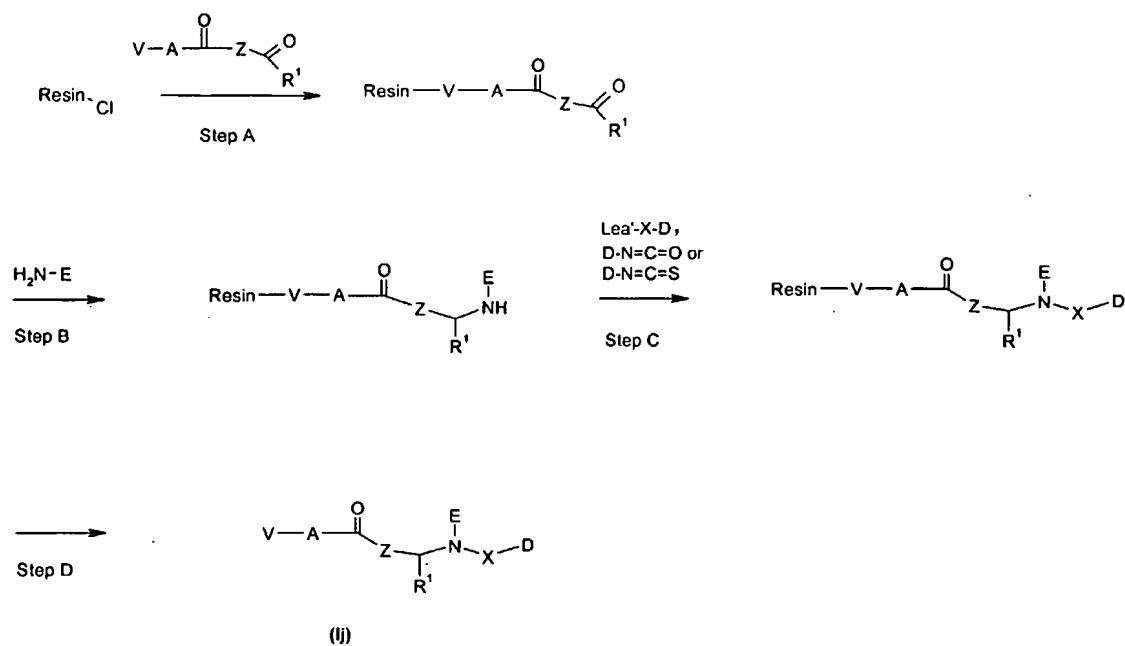
10 HPLC-MS (method B): *m/z*: 548, *R*_t = 8.35min

MA: Calc for C₂₈H₃₅Cl₂N₃O₄:

61.31% C, 6.43% H, 7.66% N; Found

61.20% C, 6.59% H, 7.34% N.

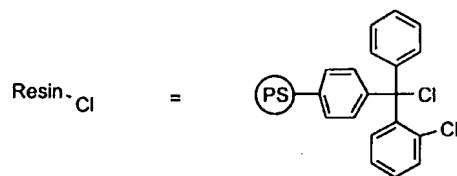
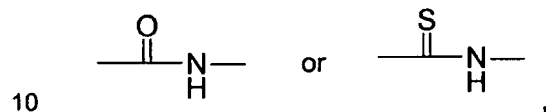
General procedure (L) for the solid phase synthesis of compounds of the general formula (II):



5 wherein

A, V, Z, R¹, E and D are as defined for formula (I),

X is



wherein PS is polystyrene

, and

Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of V-A-Z-C(O)R¹ in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotriylchloride.

Step B:

Step B is identical to step C of general procedure (T).

Step C:

Step C is identical to step D of general procedure (T).

Step D:

Step D is identical to step E of general procedure (T).

Preparation of starting materials D-N=C=O:N,N-Dimethyl-3-nitro-benzenesulfonamide

3-Nitrobenzenesulfonyl chloride (22.8 mmol, 5.05 g) was dissolved in dry THF (50 mL). Dimethylamine in THF (2M, 34 mL) was added and the mixture was refluxed for 2 hours. Upon cooling, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (250 mL), washed with water (3 x 50 mL) and dried over MgSO₄. Evaporation of the solvent afforded the title compound.

1-(3-Nitrobenzenesulfonyl)piperidine was prepared as described above using piperidine instead of dimethylamine.

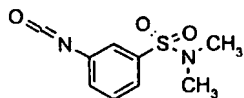
3-Amino-N,N-dimethylbenzenesulfonamide

To a solution of the above N,N-dimethyl-3-nitro-benzenesulfonamide (20.4 mmol, 4.7 g) in ethanol (50 mL) was added SnCl₂ (105 mmol, 19.9 g) and the mixture was refluxed for 1

hour. Upon cooling, the solvent was removed in vacuo. Ethyl acetate (200 mL) and NaHCO₃ (sat, 100 mL) were added to the residue followed by another 200 mL ethyl acetate and 500 mL water. The phases were separated and the organic phase was washed twice with water. The organic phase was filtered, washed with water (2 x 100 mL) dried over MgSO₄ and
5 evaporated to leave the title compound.

3-(Piperidine-1-sulfonyl)phenylamine was prepared as described above from 1-(3-nitrobenzenesulfonyl)piperidine.

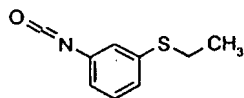
10 3-Isocyanato-*N,N*-dimethylbenzenesulfonamide



To a slurry of the above 3-amino-*N,N*-dimethylbenzenesulfonamide (3.26 g, 16 mmol) in toluene (200 mL) was added triphosgene (1.67 g) and the mixture was refluxed 16 h and
15 evaporated. The residue was used without further purification.

1-(3-Isocyanatobenzenesulfonyl)piperidine was prepared as described above from 3-piperidine-1-sulfonyl)phenylamine.

20 1-Ethylsulfanyl-3-isocyanatobenzene



To a solution of 3-aminothiophenol (40 mmol, 5 g) in DMF (50 mL) was added K₂CO₃ (4.8 mmol, 6.63 g) and 2.98 mL bromoethane. The mixture was stirred over night at 25°C and
25 poured into 200 mL ice water. 200 mL ethylacetate was added and the phases were separated. The aqueous phase was extracted with 100 mL ethylacetate and the combined organic extracts were dried over MgSO₄. Evaporation of the solvent and re-dissolving the residue in ethyl acetate (100 mL) and HCl in ethyl acetate (2M, 20 mL) afforded 3-ethylsulfanylphenylamine hydrochloride, which was collected by filtration.

30

To a slurry of the above 3-ethylsulfanylphenylamine hydrochloride (31.6 mmol, 6 g) in toluene (100 mL) was added diphosgene (trichloromethyl chloroformate, 158 mmol, 31.3 g) and

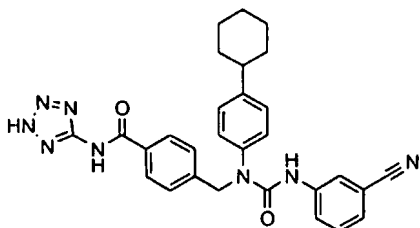
the mixture was refluxed for 2 hours affording a clear solution. The solvent was removed in vacuo and the residue was used without further purification.

The other starting materials used in the following examples were prepared in a similar way.

5

EXAMPLE 256 (general procedure (L))

4-[3-(3-Cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10 Step A: Resin bound 4-formyl-N-(2H-tetrazol-5-yl)benzamide

150 μ mol 4-Formyl-N-(2H-tetrazol-5-yl)benzamide was dissolved in a mixture of 250 μ L dichloromethane, 250 μ L DMF and 100 μ L diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

15

Step B: Resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide

The above resin bound 4-formyl-N-(2H-tetrazol-5-yl)benzamide (50 mg) was treated with a 0.5 M solution of 4-cyclohexylaniline (0.25 mmol, 41.25 mg) in a mixture of DMF and trimethylorthoformate (1:1, 0.5 mL) and glacial acetic acid (50 μ L) for 1 hour at 25°C followed by sodium cyanoborohydride (250 μ mol, 16 mg) dissolved in a mixture of DMF and methanol (1:1, 0.25 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of DMF and methanol (1:1, 2x1 mL), 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

25

Step C: Resin bound 4-[3-(3-cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

200 μ mol 3-cyanophenylisocyanate dissolved in 500 μ L dichloroethane was added to the above resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg). Shaking the mixture for 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

30

Step D: 4-[3-(3-Cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

The above resin bound 4-[3-(3-cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg) was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 μ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction per minute. The process was monitored using a UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

15

Optionally, the compound can be purified by recrystallisation from eg acetonitrile.

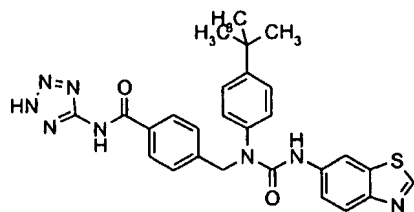
¹H NMR (300 MHz, DMSO-*d*₆): δ 12.35 (s br, 1H); 8.58 (s, 1H); 8.05 (d, 2H); 7.95 (s, 1H); 7.73 (d, 1H); 7.50-7.38 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

20

HPLC-MS (method B): m/z = 521, R_t = 7.60 min.

EXAMPLE 257 (general procedure (L))

25 4-[3-Benzothiazol-6-yl-1-(4-*tert*-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



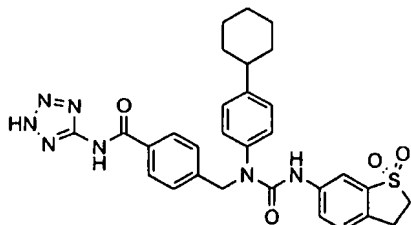
¹H NMR (DMSO-*d*₆): δ 8.5 (s, 1H); 8.28 (s, 1H); 8.05 (d, 2H); 7.93 (d, 2H); 7.55 (d, 1H); 7.48 (d, 2H); 7.43 (d, 2H); 7.22 (d, 2H); 5.03 (s, 2H); 1.28 (s, 9H).

30

HPLC-MS (Method B): m/z = 527 ($M+1$). R_t = 6.47 min.

EXAMPLE 258 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(1,1-dioxo-2,3-dihydro-1H-1-benzo[b]thiophen-6-yl)ureido-methyl]-N-(2H-tetrazol-5-yl)benzamide



5

The benzothiophene moiety was synthesized from commercially available 6-amino-1,1-dioxo-1H-1-benzo[b]thiophene using Pd/C and H₂ employing methods known by those skilled in the art. The aniline was converted to an isocyanate by methods mentioned previously.

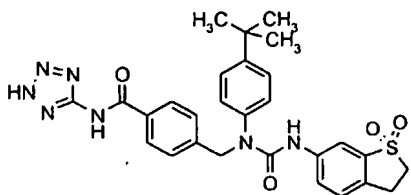
10

¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.60 (s, 1H); 8.05 (s, 2H); 7.88 (s, 1H); 7.68 (d, 1H); 7.45 (d, 2H); 7.39 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 3.58 (t, 2H); 3.30 (t, 2H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

15 HPLC-MS (Method B): *m/z* = 586 (M+1). *R*_t = 7.88 min.

EXAMPLE 259 (general procedure (L))

4-[1-(4-*tert*-Butylphenyl)-3-(1,1-dioxo-2,3-dihydro-1H-benzo[b]thiophen-6-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

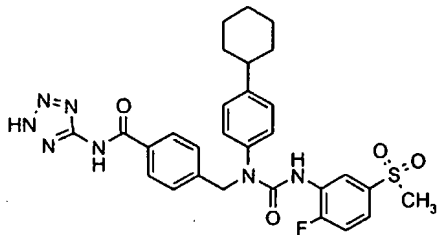
¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.65 (s, 1H); 8.05 (s, 2H); 7.88 (s, 1H); 7.60 (d, 1H); 7.48 (d, 2H); 7.45-7.38 (m, 3H); 7.22 (d, 2H); 5.00 (s, 2H); 3.58 (t, 2H); 3.34 (t, 2H); 1.32 (s, 9H).

25

HPLC-MS (Method B): *m/z* = 560 (M+1). *R*_t = 7.58 min.

EXAMPLE 260 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(2-fluoro-5-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

2-Fluoro-5-methylsulfonylphenyl isocyanate was prepared from the corresponding 2-fluoro-5-methylsulfonyl-1-nitrobenzene via reduction to the corresponding aniline as described previously.

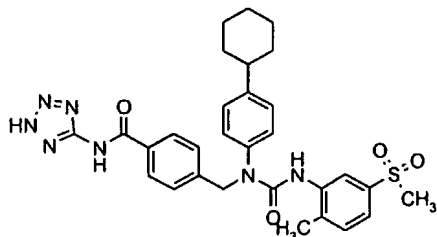
10 ¹H NMR (DMSO-*d*₆): δ 11.50 (s br, 1H); 8.30 (d, 1H); 8.00 (d, 2H); 7.90 (s, 1H); 7.65 (m, 1H); 7.50-7.40 (m, 3H); 7.25 (s, 4H); 5.05 (s, 2H); 3.18 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): *m/z* = 592 (M+1). *R*_t = 7.04 min.

15

EXAMPLE 261 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(5-methylsulfonyl-2-methylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

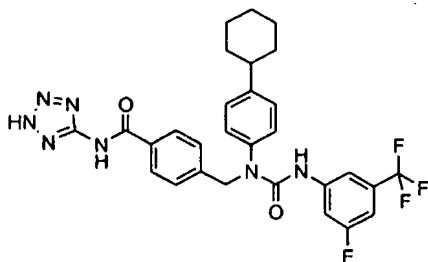
5-Methylsulfonyl-2-methylphenyl isocyanate was prepared from the corresponding 5-methylsulfonyl-2-methyl-1-nitrobenzene via reduction to the corresponding aniline followed by conversion to the isocyanate as described previously.

25 ¹H NMR (DMSO-*d*₆): δ 12.10 (s br, 1H); 8.15 (s, 1H); 8.05 (d, 2H); 7.62 (m, 6H); 7.28 (dd, 4H); 5.03 (s, 2H); 3.15 (s, 3H); 2.10 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): m/z = 588 ($M+1$). R_t = 7.10 min.

EXAMPLE 262 (general procedure (L))

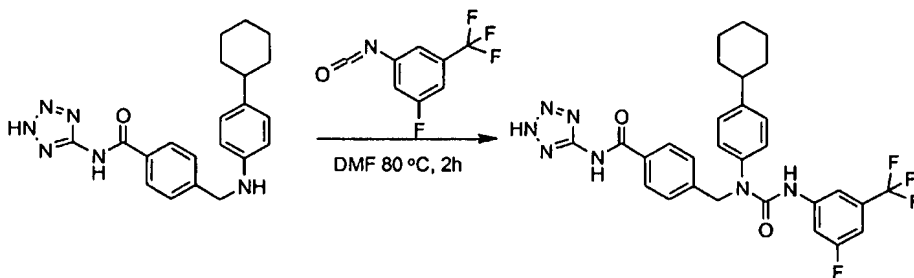
- 5 4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



- ^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (s, 1H); 8.82 (s, 1H); 8.08 (d, 2H); 7.75 (m, 2H); 7.45 (d, 2H);
10 7.25-7.15 (m, 5H); 5.02 (s, 2H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): m/z = 582 ($M+1$). R_t = 8.05 min.

Alternative method for the preparation of the title compound:



15

Preparation of 3-fluoro-5-trifluoromethylphenylisocyanate:

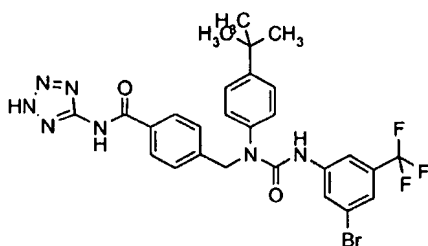
- 3-Fluoro-5-trifluoromethylaniline (2 g, 11.2 mmol) was dissolved in 20 mL diethylether and added concentrated hydrochloric acid (37%, 1.5 mL, 18 mmol). Upon stirring for 1 hour at
20 25°C the solvent was removed in vacuo and the white solid was stripped with toluene (3 x 20 mL). Diphosgene (20 mL) was added to the hydrochloride salt and the mixture was refluxed over night. Excess diphosgene was removed in vacuo and the clear oil was stripped with toluene (3 x 20 mL). The obtained isocyanate was used without further purification.

Preparation of 4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide:

A slurry of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (3 g, 7.96 mmol) in DMF (50 mL) was added to the above 3-fluoro-5-trifluoromethylphenylisocyanate and the mixture was heated to 80°C. After 2 hours the reaction was allowed to cool to 25°C and acetonitrile (500 mL) was added. The mixture was filtered, the precipitate was discarded and the filtrate evaporated. The residue was refluxed in acetonitrile (75 mL) and allowed to cool to 25°C. After filtration, a new precipitate was formed affording the title compound (850 mg).

EXAMPLE 263 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

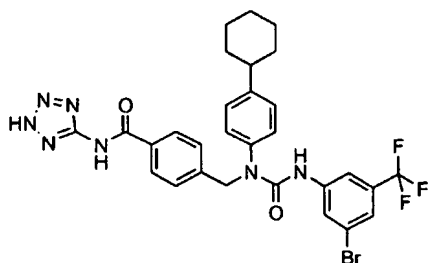


HPLC-MS (Method B): m/z = 617 ($M+1$). R_t = 7.95 min.

^1H NMR (DMSO): δ 12.40 (s, 1H); 8.80 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50 (s, 1H); 7.49 (d, 2H); 7.42 (d, 2H); 7.23 (d, 2H); 5.02 (s, 2H); 1.32 (s, 9H).

EXAMPLE 264 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method B): $m/z = 642$ ($M+1$). $R_t = 8.45$ min.

Alternative method for the preparation of the title compound:

5 Preparation of 3-bromo-5-trifluoromethylphenylisocyanate:

3-Bromo-5-trifluoromethylaniline (2.16 g, 9 mmol) was dissolved in 20 mL diethylether and added concentrated hydrochloric acid (37%, 1.5 mL, 18 mmol). Upon stirring for 1 hour at 25°C the solvent was removed in vacuo and the white solid was stripped with toluene (3 x 20 mL). Diphosgene (13 mL) was added to the ammonium chloride salt and the mixture was re-
10 fluxed for 3.5 hours until no solid material precipitated on cooling. Excess diphosgene was removed in vacuo and the clear oil was stripped with toluene (3 x 20 mL). The obtained isocyanate was used without further purification.

15 Preparation of 4-[3-(3-bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide:

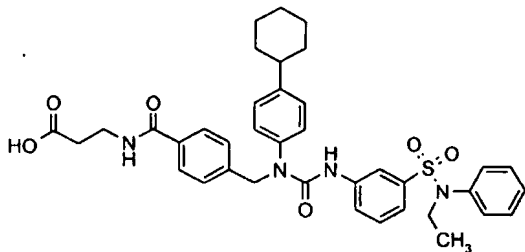
The above isocyanate was dissolved in DMF (20 mL) and added 4-[(4-cyclohexylphenyl-amino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (1.88 g, 5 mmol) and the mixture was heated at 80°C. After 1 hour the reaction was allowed to cool to 25°C and the solvent was evaporated. The residue was refluxed in acetonitrile (10 mL) and allowed to cool to 25°C. The de-
20 sired product was isolated by filtration and dried in vacuo (2.5 g).

¹H NMR (DMSO): δ 12.35 (s, 1H); 8.75 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50 (s, 1H); 7.48 (d, 2H); 7.23 (s, 4H); 5.00 (s, 2H); 1.85-1.65 (m, 5H); 1.45 -1.15 (m, 5H).

25 HPLC-MS (Method F): $m/z = 642$ ($M+1$). $R_t = 5.67$ min.

EXAMPLE 265 (general procedure (L))

3-(4-{1-(4-Cyclohexylphenyl)-3-[3-(ethylphenylsulfamoyl)phenyl]ureidomethyl}benzoylamino)-propionic acid



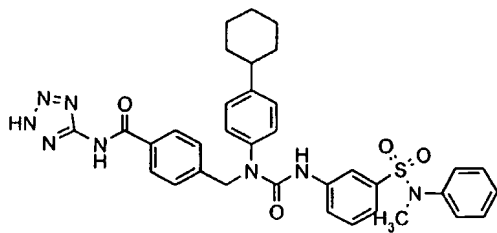
5

HPLC-MS (Method B): m/z = 683 ($M+1$). R_t = 7.60 min.

EXAMPLE 266 (general procedure (L))

4-{1-(4-Cyclohexylphenyl)-3-[3-(methylphenylsulfamoyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide

10

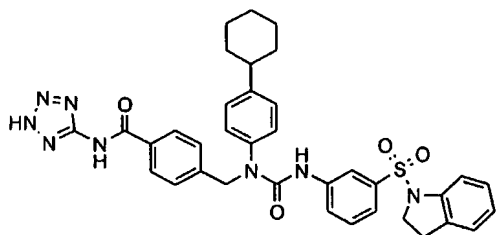


HPLC-MS (Method B): m/z = 665 ($M+1$). R_t = 7.67 min.

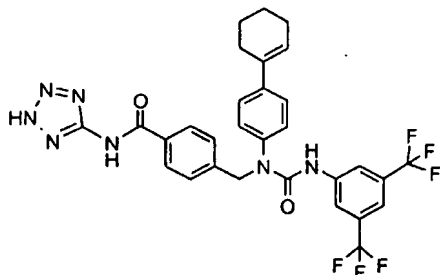
EXAMPLE 267 (general procedure (L))

4-{1-(4-Cyclohexylphenyl)-3-[3-(2,3-dihydroindole-1-sulfonyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide

15

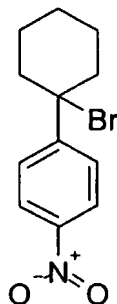


20 HPLC-MS (Method B): m/z = 677 ($M+1$). R_t = 7.75 min.

EXAMPLE 268 (general procedure (L))**4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

5

The starting material 4-(cyclohex-1-enyl)phenylamine was prepared in the following way:

Step 1: 1-(1-Bromocyclohexyl)-4-nitrobenzene

10

4-Cyclohexylnitrobenzene (22.6 g, 0.11 mol) and *N*-bromosuccinimide (21.6 g, 0.12 mol) were suspended in tetrachloromethane (200 mL) and a catalytic amount of dibenzoylperoxide was added. The reaction mixture was stirred at 80°C for 4.5 hours. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (400 mL) and washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (200 mL) and the combined organic phases were washed with water (3 x 150 mL), dried over MgSO₄ and concentrated in vacuo. The residue was crystallised from ethyl acetate and heptane to give 18.4 g of 1-(bromocyclohexyl)-4-nitrobenzene.

15

¹H NMR (DMSO-*d*₆): δ 1.29-1.40 (1H,m), 1.60-1.71 (3H,d), 1.73-1.85 (2H,m), 2.06-2.18 (2H,m), 2.55 (2H,m), 7.92 (2H,d), 8.34 (2H,d).

20

M.p.: 83.5-85.5°C.

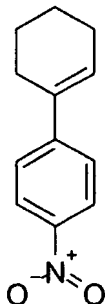
MA: calc

50.72% C, 4.97% H, 4.93% N; Found

50.65% C, 5.10% H, 4.91% N.

5

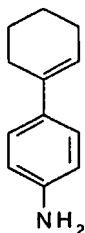
Step 2: 1-Cyclohex-1-enyl-4-nitrobenzene



10 1-(Bromocyclohexyl)-4-nitrobenzene (18.4 g, 64.8 mmol), lithium carbonate (5.3 g, 71.2 mmol), and lithium bromide (6.2 g, 71.2 mmol) were reacted together in DMF (100 mL) for 2 hours at 160°C. The reaction mixture was cooled to 20°C, diluted with ethyl acetate (500 mL), and washed with water (300 mL). The aqueous phase was extracted with ethyl acetate (200 mL) and the combined organic phases were washed with water (3 x 150 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified on silica (350 g) using ethyl
15 acetate and heptane (1:9) as eluent to give 11.7 g of 1-cyclohex-1-enyl-4-nitrobenzene.

¹H NMR (DMSO-*d*₆): δ 1.57-1.69 (2H,m), 1.60-1.70 (2H,m), 2.18-2.29 (2H,m), 2.38-2.46 (2H,m), 6.46 (1H,t), 7.67 (2H,d), 8.17 (2H,d).

20 Step 3: 4-(Cyclohex-1-enyl)phenylamine



1-Cyclohex-1-enyl-4-nitrobenzene (11.7 g, 57.6 mmol) was dissolved in hot absolute ethanol (170 mL). Stannous chloride (65 g, 288 mmol) was added and the reaction mixture was

stirred at reflux temperature for 1.5 hours. The reaction mixture was concentrated in vacuo and the residue was added ethyl acetate (700 mL) and water (700 mL), and neutralised to pH 7 with sodium hydroxide (4 N). Ethyl acetate (150 mL) was added and the mixture was filtered through celite. The organic phase of the filtrate was washed with water and a saturated solution of sodium chloride, dried over MgSO₄, and concentrated in vacuo. The residue was purified on silica (200 g) using ethyl acetate and heptane (1:4) as eluent to give 7.4 g of 4-(cyclohex-1-enyl)phenylamine.

HPLC-MS (method B): m/z: 174, R_t = 4.05 min.

10

¹H NMR (DMSO-*d*₆): δ 1.52-1.60 (2H,m), 1.63-1.72 (2H,m), 2.13 (2H,m), 2.28 (2H,m), 5.0 (2H,s), 5.90 (1H,t), 6.50 (2H,d), 7.08 (2H,d).

The title compound was prepared using 4-(cyclohex-1-enyl)phenylamine in step B.

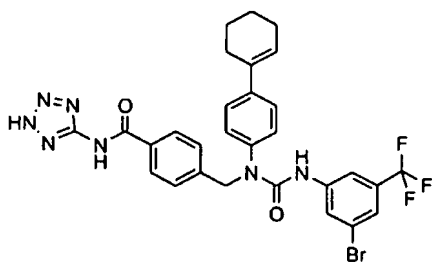
15

¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.92 (s, 1H); 8.28 (s, 2H); 8.04 (d, 2H); 7.61 (s, 1H); 7.48 (d, 2H); 7.46 (d, 2H); 7.25 (d, 2H); 6.20 (s br, 1H); 5.03 (s, 2H); 2.38 (m br, 2H); 2.18 (m br, 2H); 1.71 (m br, 2H); 1.60 (m br, 2H).

20 HPLC-MS (Method B): m/z = 630 (M+1). R_t = 8.25 min.

EXAMPLE 269 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



25

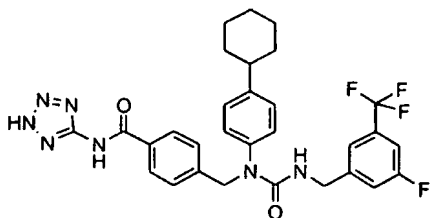
¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.75 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50-7.35 (m, 5H); 7.25 (d, 2H); 6.20 (s br, 1H); 5.03 (s, 2H); 2.35 (m br, 2H); 2.15 (m br, 2H); 1.72 (m br, 2H); 1.60 (m br, 2H)

30

HPLC-MS (Method B): m/z = 641 ($M+1$). R_t = 8.27 min.

EXAMPLE 270 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylbenzyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

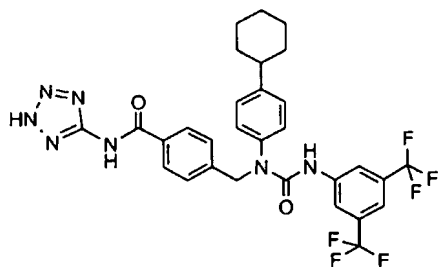


^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (s, 1H); 8.04 (d, 2H); 7.53 (d, 1H); 7.45 (s, 1H); 7.38 (d, 2H); 7.24 (d, 2H); 7.12 (d, 2H); 6.69 (t, 1H); 4.90 (s, 2H); 4.30 (d, 2H); 1.80-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): m/z = 596 ($M+1$). R_t = 7.70 min.

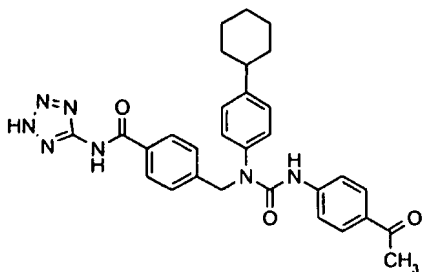
EXAMPLE 271 (general procedure (L))

4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.95 (s, 1H); 8.25 (s, 2H); 8.05 (d, 2H); 7.62 (s, 1H); 7.45 (d, 2H); 7.24 (s, 4H); 5.02 (s, 2H); 1.82-1.65 (m, 5H); 1.50-1.15 (m, 5H)

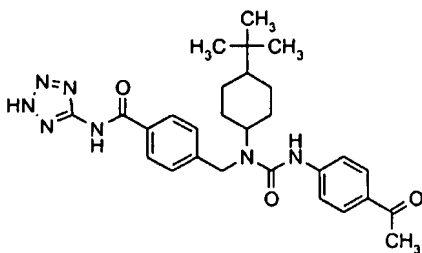
HPLC-MS (Method B): m/z = 632 ($M+1$). R_t = 8.37 min.

EXAMPLE 272 (general procedure (L))**4-[3-(4-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

- 5 ^1H NMR (300 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.62 (s, 1H); 8.05 (d, 2H); 7.85 (d, 2H); 7.60 (d, 2H); 7.45 (d, 2H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

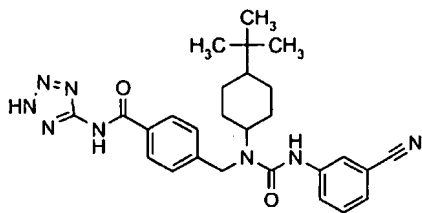
HPLC-MS (method B): m/z = 538, R_t = 7.42 min.

10 **EXAMPLE 273 (general procedure (L))**

4-[3-(4-Acetylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- ^1H NMR (300 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.85 (s, 1H); 8.05 (d, 2H); 7.85 (d, 2H);
15 7.62 (d, 2H); 7.43 (d, 2H); 4.70 (s, 2H); 4.10 (t br, 1H); 1.85-0.90 (m, 9H); 0.85 (s, 9H).

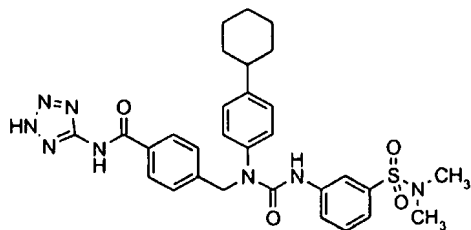
HPLC-MS (method B): m/z = 518, R_t = 7.35 min.

EXAMPLE 274 (general procedure (L))**4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-cyanophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**

- 5 ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.30 (s br, 1H); 8.73 (s, 1H); 8.05 (d, 2H); 7.93 (s, 1H); 7.75 (d, 1H); 7.50-7.30 (m, 4H); 4.65 (s, 2H); 4.08 (t br, 1H); 1.83-0.90 (m, 9H); 0.85 (s, 9H).

HPLC-MS (method B): m/z = 501, R_t = 7.62 min.

10 **EXAMPLE 275 (general procedure (L))**

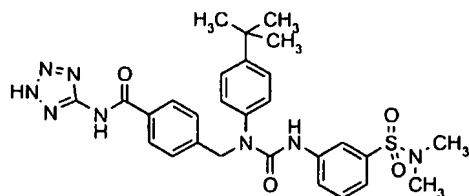
4-[1-(4-Cyclohexylphenyl)-3-(3-dimethylsulfamoylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

- 15 ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.73 (d, 1H); 7.50-7.40 (m, 3H); 7.30 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 2.60 (s, 6H) 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

HPLC-MS (method B): m/z = 603, R_t = 7.08 min.

EXAMPLE 276 (general procedure (L))

4-[1-(4-*tert*-Butylphenyl)-3-(3-dimethylsulfamoylphenyl)ureidomethyl]-N-(2*H*-tetrazol-5-yl)benzamide



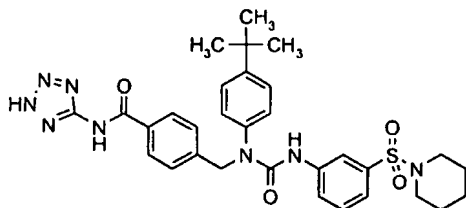
5

^1H NMR (200 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (t, 1H); 7.70 (d, 1H); 7.55-7.35 (m, 5H); 7.30 (d, 1H); 7.23 (d, 2H); 5.00 (s, 2H); 2.60 (s, 6H) 1.28 (s, 9H).

10 HPLC-MS (method B): m/z = 577, R_t = 6.48 min.

EXAMPLE 277 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-[3-(piperidine-1-sulfonyl)phenyl]ureidomethyl]-N-(2*H*-tetrazol-5-yl)benzamide



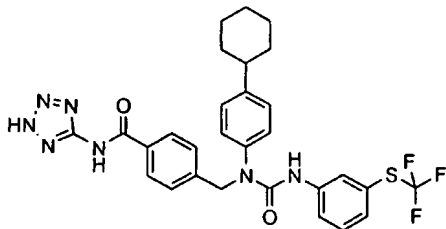
15

^1H NMR (300 MHz), (DMSO- d_6): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.70 (d, 1H); 7.52-7.18 (m, 8H); 5.00 (s, 2H); 2.90 (t, 4H) 1.65-1.35 (m, 6H); 1.28 (s, 9H).

20 HPLC-MS (method B): m/z = 617, R_t = 7.22 min.

EXAMPLE 278 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

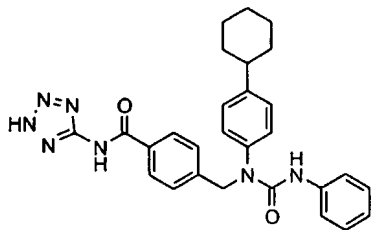
^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.58 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.70 (d, 1H); 7.45 (d, 2H); 7.40 (t, 1H); 7.30-7.15 (m, 5H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B): m/z = 596, R_t = 8.30 min.

10

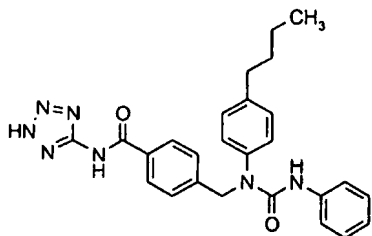
EXAMPLE 279 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-phenylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15 ^1H NMR (300 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.12 (s, 1H); 8.05 (d, 2H); 7.48 (d, 2H); 7.42 (t, 1H); 7.20 (m, 6H); 6.95 (t, 1H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

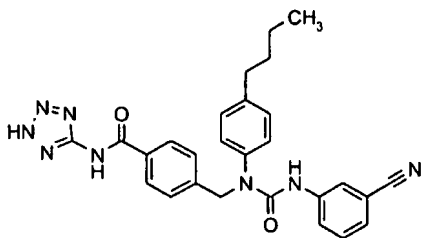
HPLC-MS (method B): m/z = 496, R_t = 7.72 min.

EXAMPLE 280 (general procedure (L))4-[1-(4-Butylphenyl)-3-phenylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5 ^1H NMR (300 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.46 (d, 2H); 7.42 (d, 2H); 7.30-7.10 (m, 6H); 6.95 (t, 1H); 5.00 (s, 2H); 2.55 (t, 2H); 1.55 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

HPLC-MS (method B): m/z = 470, R_t = 7.38 min.

10

EXAMPLE 281 (general procedure (L))4-[1-(4-Butylphenyl)-3-(3-cyanophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

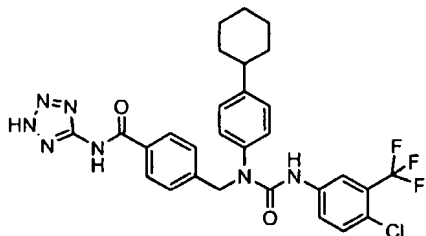
- 15 ^1H NMR (300 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.50 (s, 1H); 8.05 (d, 2H); 7.95 (s, 1H); 7.75 (d, 1H); 7.46-7.38 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 2.55 (t, 2H); 1.55 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

HPLC-MS (method B): m/z = 495, R_t = 7.28 min.

20

EXAMPLE 282 (general procedure (L))

4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d+s, 3H); 7.80 (d, 1H); 7.55 (d, 1H); 7.45 (d, 2H); 7.22 (s, 4H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B): m/z = 598, R_t = 8.55 min.

10

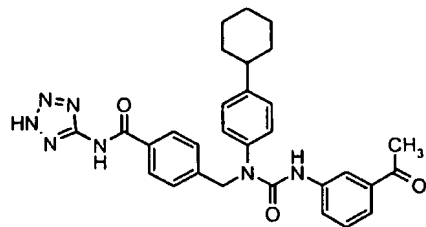
^1H NMR (MeOH- d_4): δ 1.20 – 1.50 (m, 5H), 1.75 – 1.90 (m, 5H), 2.55 (m, 1H), 5.02 (s, 2H), 7.19 (d, 2H), 7.30 (d, 2H), 7.44 – 7.50 (m, 3H), 7.60 (d, 1H), 7.90 (s, 1H), 7.99 (d, 2H).

MS (APCI, neg): 596.2, 597.2, 598.2, 375.2, 376.2.

15

EXAMPLE 283 (general procedure (L))

4-[3-(3-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

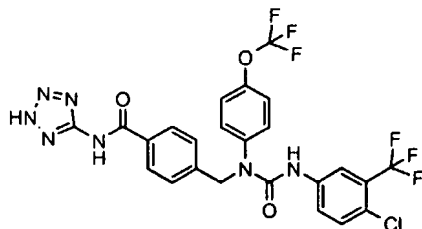
^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.48 (s, 1H); 8.05 (d+s, 3H); 7.68 (d, 1H); 7.58 (d, 1H); 7.45 (d, 2H); 7.38 (t, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 2.10 (s, 3H); 1.85-1.10 (m, 11H).

HPLC-MS (method B): m/z = 538, R_t = 7.38 min.

25

EXAMPLE 284 (general procedure (L))

4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

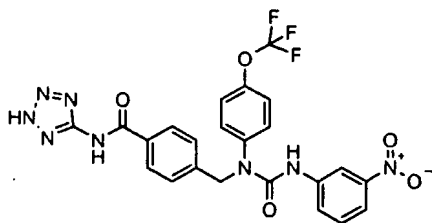
^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.90 (s, 1H); 8.05 (d+s, 3H); 7.83 (d, 1H); 7.60 (d, 1H); 7.50-7.30 (m, 6H); 5.05 (s, 2H).

HPLC-MS (method B): m/z = 600, R_t = 7.75 min.

10

EXAMPLE 285 (general procedure (L))

4-[3-(3-Nitrophenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]ureidomethyl-N-(2H-tetrazol-5-yl)benzamide

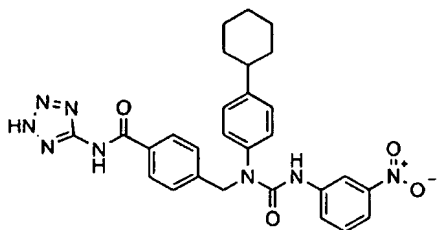


15

^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 9.00 (s, 1H); 8.48 (t, 1H); 8.05 (d, 2H); 7.92 (d, 1H); 7.82 (d, 1H); 7.60-7.30 (m, 7H); 5.05 (s, 2H).

HPLC-MS (method B): m/z = 543, R_t = 6.62 min.

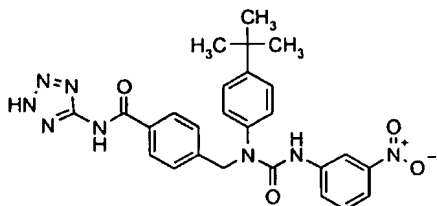
20

EXAMPLE 286 (general procedure (L))**4-[1-(4-Cyclohexylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

- 5 ^1H NMR (200 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.78 (s, 1H); 8.48 (t, 1H); 8.05 (d+s, 3H); 7.90 (d, 1H); 7.78 (d, 1H); 7.55-7.42 (m, 3H); 7.22 (s, 4H); 5.05 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B): m/z = 541, R_t = 7.67 min.

10 **EXAMPLE 287 (general procedure (L))**

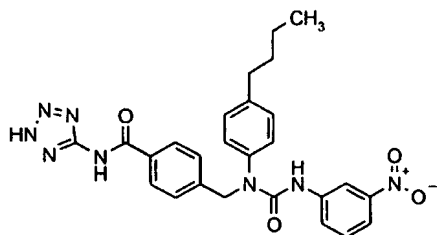
4-[1-(4-*tert*-Butylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- ^1H NMR (200 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.82 (s, 1H); 8.48 (t, 1H); 8.05 (d, 2H);
15 7.93 (d, 1H); 7.81 (d, 1H); 7.60-7.35 (m, 5H); 7.25 (d, 2H); 5.05 (s, 2H); 1.30 (s, 9H).

HPLC-MS (method B): m/z = 515, R_t = 7.13 min.

EXAMPLE 288 (general procedure (L))

20 **4-[1-(4-Butylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

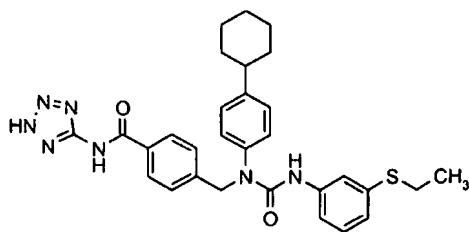


^1H NMR (200 MHz, $\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.82 (s, 1H); 8.50 (t, 1H); 8.05 (d, 2H); 7.93 (d, 1H); 7.81 (d, 1H); 7.60-7.45 (m, 3H); 7.20 (s, 4H); 5.03 (s, 2H); 2.60 (t, 2H); 1.55 (k, 2H); 1.35 (sx, 2H); 0.90 (t, 3H).

5 HPLC-MS (method B): m/z = 515, R_t = 7.33 min.

EXAMPLE 289 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-ethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

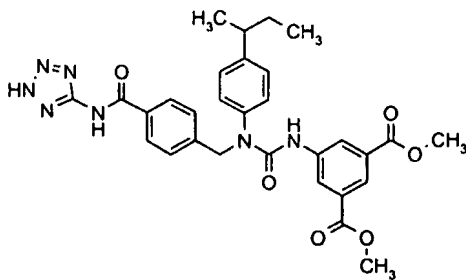


10

HPLC-MS (method B): m/z = 556, R_t = 8.07 min.

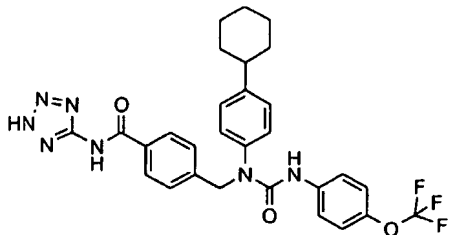
EXAMPLE 290 (general procedure (L))

15 5-[3-(4-sec-Butylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]ureidoisophthalic acid dimethyl ester



20

HPLC-MS (method B): m/z = 586, R_t = 7.23 min.

EXAMPLE 291 (general procedure (L))4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

5

^1H NMR (DMSO- d_6): δ 1.1-1.4 (5H, m), 1.65-1.85 (5H, m), 5.00 (2H, s), 7.2 (6H, m), 7.46 (2H, d), 7.55 (2H, d), 8.04 (2H, d), 8.43 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): R_t = 8.22 min, m/z = 580 ($M + 1$).

10

Alternative method for the preparation of the title compound:

To a solution of 4-carboxybenzaldehyde (40.2 g, 0.27 mol) in DMF (400 mL) was added *N*-ethyl-*N'*-3-dimethylaminopropylcarbodiimide (65.5 g, 0.33 mol) followed by 5-aminotetrazol monohydrate (36.6 g, 0.35 mol). The mixture was stirred for 24 hours at ambient temperature. The reaction volume was then reduced to one half by rotary evapoation, and water (800 mL) was added. The precipitate was collected by filtration, washed with cold acetonitrile and dried overnight in a vacuum oven to afford 46.0 g (80%) of 4-formyl-*N*-(2H-tetrazol-5-yl)benzamide.

15

20 ^1H NMR (DMSO- d_6): δ 8.08 (d, 2H); 8.26 (d, 2H); 10.15 (s, 1H); 12.68 (bs, 1H).

4-Formyl-*N*-(2H-tetrazol-5-yl)benzamide (8.94 g, 41.2 mmol) was dissolved in DMF (50 mL) by gentle heating. A solution of 4-cyclohexylaniline (7.20 g, 41.2 mmol) in methanol (100 mL) was added and a turbid suspension was formed. The suspension was heated to 70°C for 1 hour. Acetic acid (50 mL) and sodium cyanoborohydride (2.0 g, 31.7 mmol) was then added. The turbid suspension was heated to 70°C for an additional hour, before being cooled to 0°C on an ice bath. The insoluble material was collected by filtration and washed twice with water, before being dried overnight in a vacuum oven to afford 12.94 g (83.5%) of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2H-tetrazol-5-yl)benzamide.

25

30

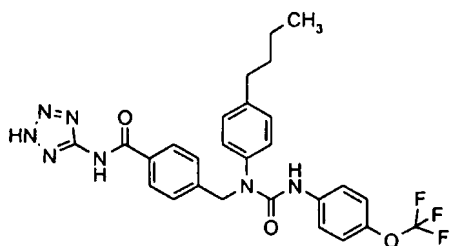
¹H NMR (DMSO-*d*₆): δ 1.28 (m, 5H); 1.68 (m, 5H); 2.28 (m, 1H); 4.32 (s, 2H); 6.17 (bs, 1H); 6.48 (d, 2H); 6.88 (d, 2H); 7.52 (d, 2H); 8.03 (d, 2H); 12.30 (s, 1H).

To a suspension of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide
5 (12.5 g, 33.2 mmol) in DMF (120 mL) was added 4-trifluoromethoxyphenyl isocyanate (6.8 g, 33.2 mmol). A clear solution was obtained upon heating to 80°C. After 30 minutes heating at 80°C, the solution was allowed to cool to room temperature. Solvent was removed by rotary evaporation, and the residual oil taken up into hot acetonitrile (500 mL). The title material, which separated out upon cooling, was collected by filtration and washed twice with cold ace-
10 tonitrile to afford 15.32 g (80.0%) of the title compound.

¹H NMR (DMSO-*d*₆): δ 1.35 (m, 5H); 1.78 (m, 5H); 2.42 (m, 1H); 4.96 (s, 2H); 7.20 (s, 4H); 7.24 (d, 2H); 7.47 (d, 2H); 7.55 (d, 2H); 8.02 (d, 2H); 8.44 (s, 1H); 12.35 (s, 1H).

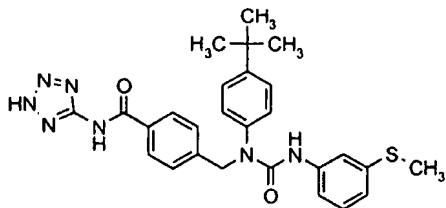
15 EXAMPLE 292 (general procedure (L))

4-[1-(4-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



20 ¹H NMR (DMSO-*d*₆): δ 0.90 (3H, t), 1.33 (2H, sextet), 1.56 (2H, pentet), 2.55 (2H, partly hidden by DMSO), 5.00 (2H, s), 7.20 (4H, s), 7.23 (2H, d), 7.45 (2H, d), 7.57 (2H, d), 8.02 (2H, d), 8.36 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): *R*_t = 7.85 min, *m/z* = 554 (*M* + 1).

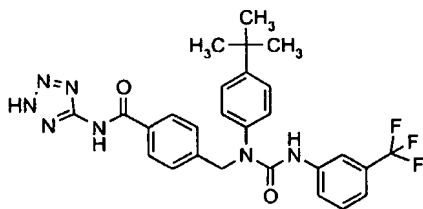
EXAMPLE 293 (general procedure (L))**4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide**

5

¹H NMR (DMSO-*d*₆): δ 1.28 (9H, s), 2.43 (3H, s), 5.01 (2H, s), 6.36 (1H, d), 7.15-7.25 (4H, m), 7.40 (3H, m), 7.48 (2H, d), 8.04 (2H, d), 8.25 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): *R*_t = 7.42 min, *m/z* = 516 (*M* + 1).

10

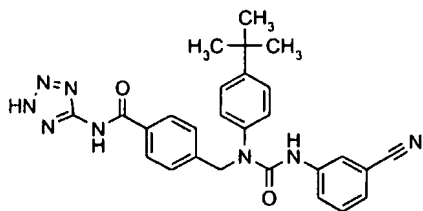
EXAMPLE 294 (general procedure (L))**4-[1-(4-*tert*-Butylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide**

15

¹H NMR (DMSO-*d*₆): δ 1.30 (9H, s), 5.01 (2H, s), 7.25 (2H, d), 7.30 (1H, d), 7.4-7.5 (5H, m), 7.75 (1H, m), 7.93 (1H, s), 8.05 (2H, d), 8.62 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): *R*_t = 7.58 min, *m/z* = 538 (*M* + 1).

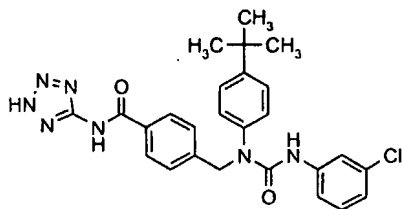
20

EXAMPLE 295 (general procedure (L))**4-[1-(4-*tert*-Butylphenyl)-3-(3-cyanophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**

- 5 ^1H NMR ($\text{DMSO}-d_6$): δ 1.28 (9H, s), 5.00 (2H, s), 7.24 (2H, d), 7.4-7.5 (6H, m), 7.77 (1H, dt), 7.94 (1H, s), 7.93 (1H, s), 8.04 (2H, d), 8.60 (1H, s), 12.3 (1H, bs).

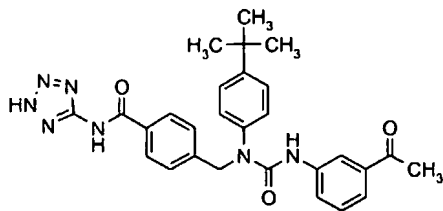
HPLC-MS (Method B): R_t = 6.83 min, m/z = 495 ($M + 1$).

10 **EXAMPLE 296 (general procedure (L))**

4-[1-(4-*tert*-Butylphenyl)-3-(3-chlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

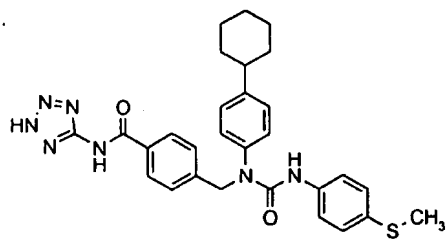
- ^1H NMR ($\text{DMSO}-d_6$): δ 1.28 (9H, s), 5.01 (2H, s), 7.00 (1H, d), 7.2-7.25 (3H, m), 7.35-7.4 (3H, m), 7.47 (2H, d), 7.64 (1H, t), 8.05 (2H, d), 8.43 (1H, s), 12.4 (1H, bs).
- 15

HPLC-MS (Method C): R_t = 5.38 min, m/z = 504 ($M + 1$).

EXAMPLE 297 (general procedure (L))**4-[3-(3-Acetylphenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**

- 5 ^1H NMR (DMSO- d_6): δ 1.28 (9H, s), 2.53 (3H, s), 5.03 (2H, s), 7.24 (2H, d), 7.4 (3H, m), 7.48 (2H, d), 7.57 (1H, d), 7.78 (1H, d), 8.0-8.05 (3H, m), 8.49 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method C): R_t = 4.75 min, m/z = 512 ($M + 1$).

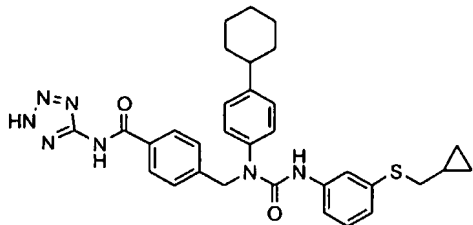
10 **EXAMPLE 298 (general procedure (L))****4-[1-(4-Cyclohexylphenyl)-3-(4-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide**

- 15 ^1H NMR (DMSO- d_6): δ 1.1-1.4 (5H, m), 1.6-1.8 (5H, m), 2.40 (3H, s), 5.00 (2H, s), 7.2 (6H, m), 7.40 (2H, d), 7.46 (2H, d), 8.04 (2H, d), 8.20 (1H, s), 8.0-8.05 (3H, m), 8.49 (1H, s), 12.3 (1H, bs).

HPLC-MS (Method C): R_t = 5.73 min, m/z = 542 ($M + 1$).

EXAMPLE 299 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopropylmethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



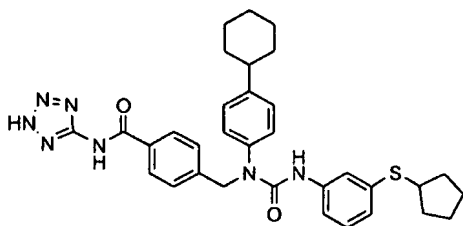
5

HPLC-MS (method B): m/z: 582, R_t = 8.28 min.

EXAMPLE 300 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopentylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

10

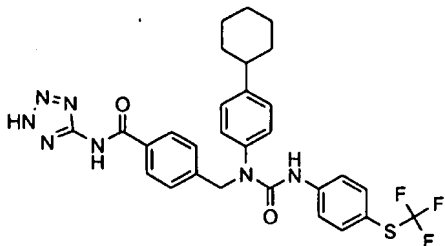


HPLC-MS (method B): m/z: 596, R_t = 8.70 min.

15

EXAMPLE 301 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



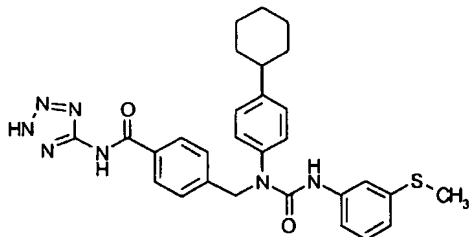
20

^1H NMR (300 MHz, DMSO- d_6): δ 8.63 (s, 1H); 8.04 (d, 2H); 7.64 (d, 2H); 7.56 (d, 2H); 7.23 (d, 2H); 7.18 (d, 2H); 4.49 (s, 2H); 1.80 (m, 4H); 1.69 (m, 1H); 1.38 (m, 4H); 1.27 (m, 1H).

HPLC-MS (method B) m/z = 596, R_t = 8.58 min.

EXAMPLE 302 (general procedure (L))

- 5 4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

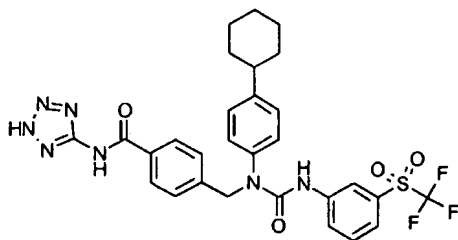


- ^1H NMR (DMSO- d_6): δ 8.22 (s, 1H), 7.95 (d, 2H), 7.40 (d, 3H), 7.25-7.10 (m, 6H), 6.83 (d, 1H), 4.97 (s, 2H), 4.02 (m, 1H), 2.42 (s, 3H), 1.85-1.15 (m, 10H).

HPLC-MS (method B): m/z : 542, R_t = 7.92 min.

EXAMPLE 303 (general procedure (L))

- 15 4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

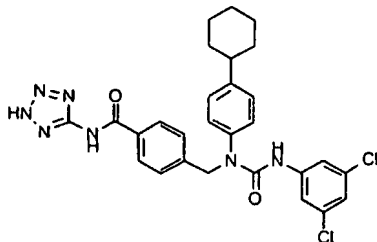


- ^1H NMR (DMSO- d_6): δ 12.4 (s, 1H), 8.90 (s, 1H), 8.32 (s, 1H), 8.11 (d, 1H), 8.03 (d, 2H), 7.70 (m, 2H), 7.45 (d, 2H), 7.23 (s, 4H), 5.00 (s, 2H), 1.85-1.15 (m, 10H).

HPLC-MS (method B): m/z : 628, R_t = 8.05 min.

EXAMPLE 304 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

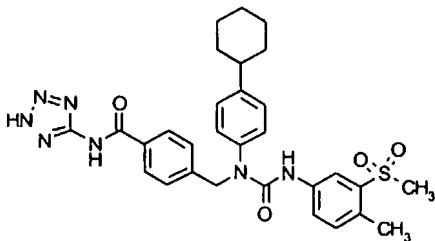
^1H NMR (DMSO- d_6): δ 12.25 (s, 1H), 8.61 (s, 1H), 8.02 (d, 2H), 7.60 (s, 2H), 7.45 (d, 2H), 7.21 (dd, 4H), 7.15 (s, 1H), 4.97 (s, 2H), 1.85-1.15 (m, 10H).

HPLC-MS (method B): m/z : 564, R_t = 8.62 min.

10

EXAMPLE 305 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonyl-4-methylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

Preparation of intermediary 3-methylsulfonyl-4-methylaniline:

Under a nitrogen atmosphere, thionylchloride (4ml, 58 mmol) and methanesulphonic acid (9 mL, 146 mmol) were refluxed for 90 min. 4-Nitrotoluene (4 g, 29 mmol) and trifluoromethanesulphonic acid (200 μL , 3 mmol) were added and the mixture was allowed to stand for 48 hours at 120°C. The mixture was cooled to 0°C and water (50 mL) was carefully added, followed by addition of ethyl acetate (150 mL). The organic phase was separated and extracted with a saturated solution of sodium hydrogencarbonate (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried (MgSO_4) and concentrated in vacuo. The residue was purified by flash chromatography (heptane/ethylacetate, 1:1) to give 0.75 g of 2-methylsulfonyl-1-methyl-4-nitrobenzene.

25

¹H NMR (400 MHz, DMSO-*d*₆): δ 2.78 (3H, s); 3.35 (3H, s); 7.78 (1H, d); 8.47(1H, dd); 8.63 (1H,s).

- 5 2-Methylsulfonyl-1-methyl-4-nitrobenzene (500 mg, 2.3 mmol) was dissolved in absolute ethanol (15 mL). Stannous chloride (2.6 g, 11.6 mmol) was added and the reaction mixture was stirred at 75°C for 4 hours. The mixture was poured into water (50 mL), pH was adjusted with a saturated solution of sodium carbonate to basic reaction, followed by addition of ethyl acetate (150 mL). The organic phase was extracted with water (2 x 50 mL), dried (MgSO₄)
10 and concentrated in vacuo to give 0.36 g of 3-methylsulfonyl-4-methylaniline as an oil.

¹H NMR (300 MHz, DMSO-*d*₆): δ 2.42 (3H, s); 3.11 (3H, s); 5.42 (2H, s); 6.75(1H, dd); 7.06 (1H, d); 7.16 (1H, d).

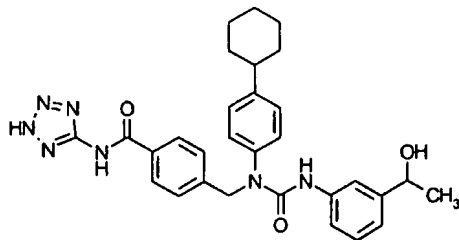
- 15 From 3-methylsulfonyl-4-methylaniline the corresponding isocyanato compound was prepared as described above. The isocyanato compound was used in step D of the general procedure (L) for the preparation of the title compound.

¹H NMR (DMSO-*d*₆): δ 12.35 (s, 1H), 8.05 (d, 2H), 7.52 (d, 2H), 7.39 (d, 2H), 6.49 (d, 1H),
20 4.35 (s, 2H), 2.30 (m, 1H), 2.09 (s, 3H), 1.85-1.15 (m, 10H).

HPLC-MS (method B): m/z: 589, R_t = 7.0 min.

EXAMPLE 306 (general procedure (L))

- 25 4-{1-(4-Cyclohexylphenyl)-3-[3-(1-hydroxyethyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide



- The title compound was prepared using 3-acetylphenylisocyanate to give 4-{1-(4-cyclohexyl-
30 phenyl)-3-[3-acetylphenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide followed by solution

phase reduction of the 3-acetyl group using sodium borohydride in methanol as reducing agent.

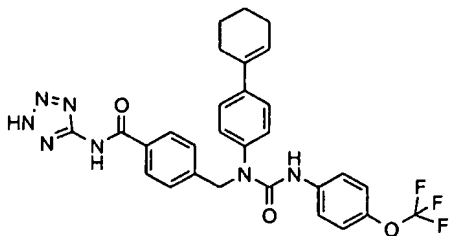
¹H NMR (DMSO-*d*₆): δ 12.35 (s, 1H), 8.15 (s, 1H), 8.03 (d, 1H), 7.46 (d, 2H), 7.39 (s, 1H),
5 7.32 (d, 1H), 7.20 (m, 5H), 6.90 (d, 1H), 5.10 (d, 1H), 5.00 (s, 2H), 4.63 (m, 1H), 1.85-1.15 (m, 13H).

HPLC-MS (method B): m/z: 540, R_t = 6.9 min.

10 MA: calculated for C₃₀H₃₃N₇O₃:
66.77% C, 6.16% H, 18.17% N; Found:
66.52% C, 6.21% H, 17.93% N.

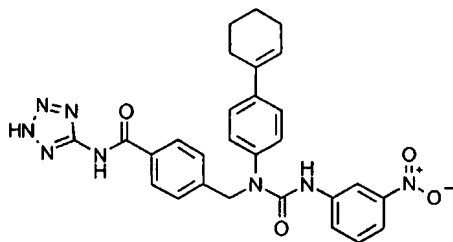
EXAMPLE 307 (general procedure (L))

15 4-[1-(4-Cyclohex-1-enylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



¹H NMR (DMSO-*d*₆): δ 8.45 (s, 1H), 7.95 (d, 2H), 7.55 (d, 2H), 7.40 (dd, 4H), 7.20 (dd, 4H),
20 6.18 (t, 1H), 5.00 (s, 2H), 2.35 (m, 2H), 2.18 (m, 2H), 1.72 (m, 2H), 1.60 (m, 2H).

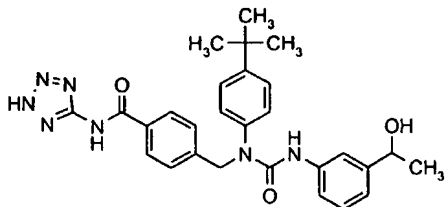
HPLC-MS (method B): m/z: 578, R_t = 7.83 min.

EXAMPLE 308 (general procedure (L))**4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

- 5 ¹H NMR (DMSO-*d*₆): δ 8.79 (s, 1H), 8.48 (s, 1H), 7.95 (m, 3H), 7.80 (d, 1H), 7.51 (t, 1H), 7.42 (dd, 4H), 7.22 (d, 2H), 6.19 (t, 1H), 5.00 (s, 2H), 2.35 (m, 2H), 2.18 (m, 2H), 1.72 (m, 2H), 1.60 (m, 2H).

HPLC-MS (method B): *m/z*: 539, *R*_t = 7.3 min.

10

EXAMPLE 309 (general procedure (L))**4-{1-(4-*tert*-Butylphenyl)-3-[3-(1-hydroxyethyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide**

15

The title compound was prepared using 3-acetylphenylisocyanate to give 4-{1-(4-*tert*-butylphenyl)-3-[3-acetylphenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide followed by solution phase reduction of the 3-acetyl group using sodium borohydride in methanol as reducing agent, before cleavage from the support.

20

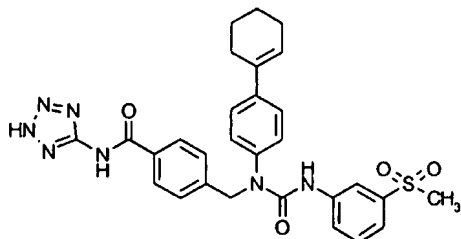
¹H NMR (DMSO-*d*₆): δ 8.18 (s, 1H), 8.03 (d, 2H), 7.48 (d, 2H), 7.39 (d, 2H), 7.32 (d, 1H), 7.20 (d, 2H), 7.15 (t, 1H), 6.90 (d, 1H), 5.10 (d, 1H), 5.00 (s, 2H), 4.63 (m, 1H), 1.3 (s, 9H).

HPLC-MS (method B): *m/z*: 514, *R*_t = 6.2 min.

25

EXAMPLE 310 (general procedure (L))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

HPLC-MS (method B): m/z: 572, R_t = 6.4 min.

^1H NMR (DMSO- d_6): δ 12.3 (s, 1H), 9.08 (s, 1H), 8.25 (s, 2H), 8.03 (d, 2H), 7.61 (s, 1H), 7.42 (d, 2H), 7.11 (s, 1H), 4.65 (s, 2H), 4.08 (m, 1H), 1.80-0.75 (m, 9H), 0.81 (s, 9H)

10

HPLC-MS (method B): m/z: 612, R_t = 8.5 min.

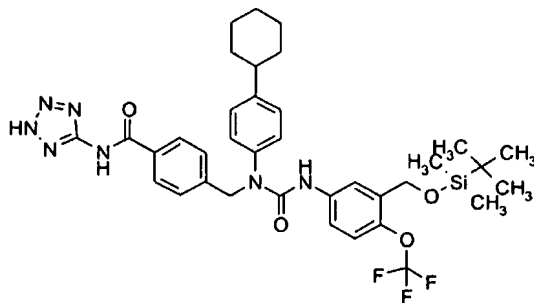
MA: calculated for $\text{C}_{28}\text{H}_{31}\text{F}_6\text{N}_7\text{O}_2$:

54.99% C; 5.11% H; 16.03% N; Found:

15 54.62% C; 5.15% H; 15.85% N.

EXAMPLE 311 (general procedure (L))

4-[3-[3-(*tert*-Butyldimethylsilanyloxymethyl)-4-trifluoromethoxyphenyl]-1-(4-cyclohexylphenyl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

Fuming nitric acid (5 mL) was cooled on an ice bath. Methyl 2-(trifluoromethoxy)benzoate (5 g, 22.7 mmol) was slowly added within 30 minutes keeping the temperature below 15°C. The reaction was then stirred at 60°C for 1 hour and 2 hours at room temperature. The mixture

was poured on ice water whereupon an oil separated. The aqueous supernatant was decanted and additional water (50 mL) was added to the oil. After neutralisation with sodium hydrogen carbonate, the mixture was extracted with ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (15 mL) once more. The combined organic phases
5 were washed with saturated sodium chloride (2 x 15 mL), dried (MgSO₄), and concentrated in vacuo to give 5.69 g of 5-nitro-2-trifluoromethoxybenzoic acid methyl ester.

¹H NMR (DMSO-*d*₆): δ 3.93 (3H, s), 7.82 (1H, d), 8.58 (1H, d), 8.67 (1H, s)

10 HPLC-MS (method B): m/z: 266; Rt = 6.0 min.

5-Nitro-2-trifluoromethoxybenzoic acid methyl ester (5.69 g, 21.5 mmol) was dissolved in ethanol 99.9% (80 mL) and stannous (II) chloride dihydrate (24.2 g, 107 mmol) was added. The suspension was stirred on an oil-bath at 75°C for 2 hours and concentrated in vacuo.
15 Ethyl acetate (100 mL) and water (50 mL) was added and pH was adjusted to pH 8 with 4N sodium hydroxide (50 mL). The liquid was decanted from the precipitation. The precipitate was washed twice with ethyl acetate. The aqueous phase was extracted twice with ethyl acetate (60 mL). The combined organic phases were washed with a saturated sodium chloride solution (2 x 100 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column
20 chromatography (120 g silica) using ethyl acetate and heptane (1:1) as eluent afforded 3.8 g of 5-amino-2-trifluoromethoxybenzoic acid methyl ester.

¹H NMR (DMSO-*d*₆): δ 3.82 (3H,s), 5.63 (2H, s), 6.79 (1H, d), 7.07 (1H, s), 7.11 (1H, d)

25 HPLC-MS (method B): m/z: 236, Rt = 4.6 min.

5-Amino-2-trifluoromethoxybenzoic acid methyl ester (3.0 g, 12.8 mmol) was dissolved in THF (20 mL) in a three-necked flask equipped with a thermometer and an addition funnel under nitrogen. Under stirring and ice-cooling lithium aluminum hydride (1M in THF, 15 mL)
30 was added dropwise within 10 minutes. Stirring was continued at room temperature for 1hr, and the reaction was concentrated in vacuo. The residue was suspended in dichloromethane (150 mL) and water (50 mL), then filtered through celite, washed with dichloromethane and water. The filtrate was separated, and the water phase was extracted once more with dichloromethane (30 mL). The combined organic phases were washed with water (2 x 20 mL),

dried (MgSO₄) and concentrated in vacuo to give 2.47 g of (5-amino-2-trifluoromethoxy-phenyl)methanol.

¹H NMR (DMSO-*d*₆): δ 3.92 (2H, d), 5.18 (1H, t), 5.28 (2H, s), 6.45 (1H, d), 6.91 (1H, d)

5

HPLC-MS (method B): m/z: 208, Rt = 7.2 min.

5-Amino-2-trifluoromethoxyphenyl)methanol (1.2 g, 5.8 mmol) was dissolved in DMF (5 mL) and imidazole (0.48 g, 7.1 mmol) and *tert*-butyldimethylsilyl chloride (0.99 g, 6.6 mmol) were added. The reaction mixture was stirred for 16 hours and water (20 mL) was added. The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with water (10 mL), citric acid (10 mL, 10%) and water (2 x 10 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (110g, silica) using ethyl acetate and heptane (1:3) as eluent to give 1.2 g of 3-(*tert*-butyldimethylsilyloxymethyl)-4-trifluoromethoxyaniline.

15

¹H NMR (DMSO-*d*₆): δ 0.82 (9H, s), 3.25 (6H, s), 4.52 (2H, s), 5.23 (2H, s), 6.41 (1H, d), 6.61 (1H, s), 6.86 (1H, d)

20 HPLC-MS (method B): m/z: 322; Rt = 7.17 min.

Triphosgene (0.09 g, 0.31 mmol) was dissolved in dichloromethane (2 mL) under nitrogen and cooled on ice. 3-(*tert*-Butyldimethylsilyloxymethyl)-4-trifluoromethoxyphenyl amine (0.3 g, 0.93 mmol) was evaporated twice with toluene and dissolved in dichloromethane (2 mL) and diisopropylethylamine (0.32 mL, 1.86 mmol) was added. This solution was then added to the solution of triphosgene, and after 2 hours at room temperature a slurry of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (0.35 g, 0.93 mmol) in DMF (6 mL) was added. Before adding 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide this was concentrated twice from toluene to remove any content of water. The mixture was stirred under nitrogen at 80°C for 2 hours and concentrated in vacuo, and the residue was extracted with dichloromethane (80 mL) and citric acid (25 mL, 10%). The aqueous phase was extracted with dichloromethane (30 mL) and the combined organic phases were washed with citrus acid (3 x 25 mL, 10%), dried and concentrated in vacuo. The residue was purified by column chromatography (35 g silica) using dichloromethane and 10% ammonia in

30

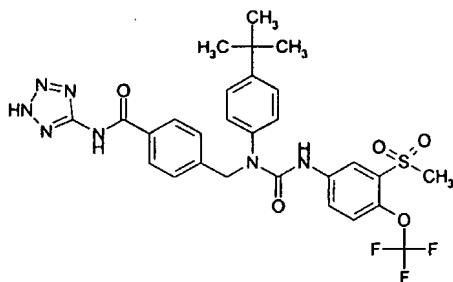
ethanol 85:15 as eluent to give 97 mg of 4-[3-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-trifluoromethoxyphenyl]-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide.

¹H NMR (DMSO-*d*₆): δ 0.08 (6H, s), 0.89 (9H, s), 1.17-1.45 (5H, m), 1.67-1.82 (5H, m), 4.67 (2H, s), 5.00 (2H, s), 7.16-7.25 (5H, m), 7.45 (3H, d), 7.63 (1H, s), 8.02 (2H, d), 8.44 (1H, s) 11.97 (1H, broad).

HPLC-MS (method B): *m/z*: 610 (without dimethyl-*tert*-butylsilyl).

10 **EXAMPLE 312 (general procedure (L))**

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



15 **Synthesis of 3-methylsulfonyl-4-trifluoromethoxyphenyl isocyanate**

To a solution of methyl iodide (59.0 g, 0.41 mol) in DMF (150 mL) was added potassium carbonate (23.0 g, 0.16 mol). 2-(Trifluoromethoxy)thiophenol (16.0 g, 0.08 mol) was added in portions during 30 minutes. The reaction mixture was then stirred vigorously overnight. Water (250 mL) was added. The reaction mixture was extracted with ethyl acetate (2 x 150 mL).

20 The combined organic phases were extracted with a 50% saturated aqueous solution of sodium chloride (4 x 100 mL), dried (MgSO₄), and concentrated in vacuo to give 15.0 g of 1-methylsulfonyl-2-trifluoromethoxybenzene.

1-Methylsulfonyl-2-trifluoromethoxybenzene (15.0 g, 72 mmol) was dissolved in dichloromethane (200 mL) and *m*-chloroperoxybenzoic acid (39.0 g, 216 mmol) was added in small portions during 30 minutes. The reaction mixture was then allowed to stand overnight. Dichloromethane (200 mL) was added followed by slow addition of sodium hydroxide (2*N*, 200 mL). The organic phase was separated and extracted with sodium hydroxide (2*N*, 3 x 150 mL), dried (MgSO₄) and concentrated in vacuo to give 15.8 g of 1-methylsulfonyl-2-trifluoromethoxybenzene.

¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, 1H); 7.71 (t, 1H); 7.48 (m, 2H) 3.23(s 1H).

MA: Calculated for C₈H₇F₃O₃S:

5 40.00 % C, 2.94 % H; Found
40.22 % C, 2.92 % H.

m.p. 44-46 °C.

10 1-Methylsulfonyl-2-trifluoromethoxybenzene (15.7 g, 65 mmol) was dissolved in concentrated
sulfuric acid (27 mL) and the solution was heated to 40 °C. Nitric acid (100%, 27 mL) was
added dropwise over 45 minutes. The reaction mixture was allowed to stand overnight at 60
°C, cooled, and then poured on crushed ice (300 mL). The precipitated product was isolated
by filtration, washed with water (10 x 50 mL) and dried (MgSO₄), affording 17.5 g of 3-
15 methylsulfonyl-4-trifluoromethoxynitrobenzene.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.69 (d, 1H); 8.64 (d, 1H); 7.95 (d, 1H) 3.45 (s 3H).

MA: calculated for C₈H₆F₃NO₅S:

20 33.69% C, 2.12% H, 4.91% N; Found
33.91% C, 2.08% H, 4.92% N.

m.p. 102-104 °C.

25 3-Methylsulfonyl-4-trifluoromethoxynitrobenzene (17.5g) was dissolved in methanol (400 mL)
followed by addition of palladium on carbon (10%, 50% water, 3.2 g). The reaction mixture
was hydrogenated for 17 hours at 1 atm of hydrogen, filtered and concentrated in vacuo to
give 14.3 g of 3-methylsulfonyl-4-trifluoromethoxyaniline.

30 ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.26 (d, 1H); 7.14 (d, 1H); 6.85 (dd, 1H) 5.89(s, 2H) 3.21(s,
3H).

MA: calculated for C₈H₈F₃NO₃S:

35 37.65% C, 3.16% H, 5.49% N; Found,
37.65% C, 3.14% H, 5.45% N.

m.p. 106-109 °C.

To 3-methylsulfonyl-4-trifluoromethoxyaniline (2.0 mmol, 500 mg) dissolved in ethyl acetate (6 ml) was added 3N HCl in ethyl acetate (5 ml) followed by concentration in vacuo. The residue was treated with toluene (3 x 5 mL) and each time concentrated in vacuo. To the residue was added toluene (10 mL) and trichloromethyl chloroformate (6 mmol, 0.73 mL), and under a N₂ atmosphere the suspension was gently refluxed for 2 hours at 120°C. Additional trichloromethyl chloroformate (6 mmol, 0.73 mL) was added and refluxing was continued overnight. The reaction mixture was concentrated in vacuo to afford 3-methylsulfonyl-4-trifluoromethoxyphenyl isocyanate.

Synthesis of 4-[1-(4-*tert*-butylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

3-methylsulfonyl-4-trifluoromethoxyphenyl isocyanate was used without further characterization for the preparation of the title compound.

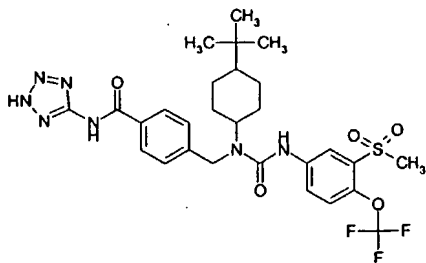
¹H NMR (300 MHz, DMSO-*d*₆): δ 10.72 (s, 1H); 10.38 (s, 1H); 8.51 (d, 1H); 8.28 (dd, 1H); 7.93 (d, 2H), 7.67 (dd 1H), 7.46 (d, 2H), 7.42 (d, 2H), 7.23 (d, 2H); 5.08 (s, 2H); 1.28 (s, 9H).

HPLC-MS (method B) *m/z* = 632, *R*_t = 6.98 min.

The following examples were made similarly as described in example 312.

EXAMPLE 313 (general procedure (L))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



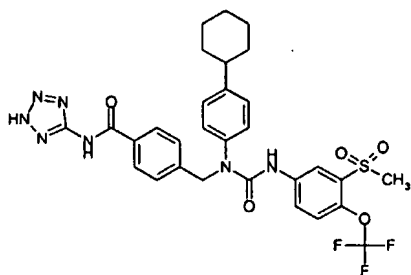
^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.25 (s, br, 1H); 8.95 (s, 1H); 8.19 (d, 1H), 8.04 (d 2H), 7.42 (d, 2H), 4.68 (s, 2H), 4.09 (t, br, 1H); 3.28 (s, 3H); 0.82 (s, 9H).

HPLC-MS (method B) m/z = 638, R_t = 7.37 min.

5

EXAMPLE 314 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10

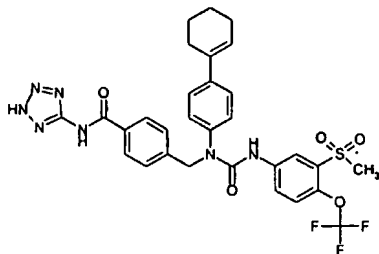
^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 10.72 (s, 1H); 10.38 (s, 1H); 8.51 (d, 1H), 8.28 (dd 1H), 7.93 (d, 2H), 7.67 (dd, 1H), 7.46 (d, 2H) 7.23 (s, 4H); 5.06 (s, 2H);

HPLC-MS (method B) m/z = 658, R_t = 7.47 min.

15

EXAMPLE 315 (general procedure (L))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

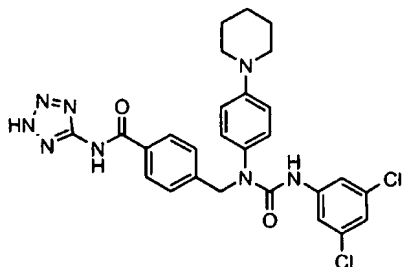
^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.72 (s, 1H); 10.46 (s, 1H), 8.52 (d, 1H); 8.28 (dd, 1H), 7.93 (d, 2H), 7.46 (d, 2H), 7.41 (d, 2H), 7.23 (d, 2H), 6.18 (s, 1H), 3.27 (m, 2H), 2.18 (m, 2H), 1.71 (m, 2H), 1.6 (m, 2H)

HPLC-MS (method B) m/z = 656, R_t = 7.23 min.

25

EXAMPLE 316 (general procedure (L))

4-[3-(3,5-Dichlorophenyl)-1-(4-piperidin-1-ylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



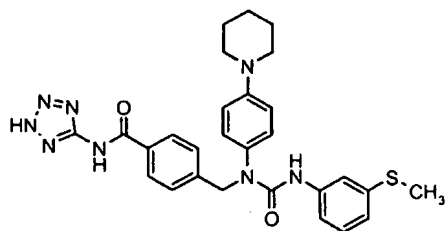
5

^1H NMR ($\text{DMSO}-d_6$): δ 4.90 (2H, s), 6.91 (2H, d), 7.07 (2H, d), 7.13 (1H, t), 7.44 (2H, d), 7.65 (2H, d), 8.02 (2H, d), 8.28 (1H, s).

10 HPLC-MS (Method B): m/z = 565 ($M+1$), R_t = 4.37 min.

EXAMPLE 317 (general procedure (L))

4-[3-(3-Methylsulfonylphenyl)-1-(4-piperidin-1-ylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



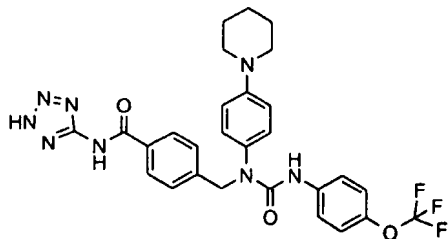
15

^1H NMR ($\text{DMSO}-d_6$): δ 4.97 (2H, s), 6.83 (1H, d), 6.95-7.25 (6H, m), 7.4-7.5 (3H, m), 7.95 (1H, s), 8.00 (2H, d), 12.4 (1H, s).

20 HPLC-MS (Method B): m/z = 543 ($M+1$), R_t = 4.72 min.

EXAMPLE 318 (general procedure (L))

4-[1-(4-Piperidin-1-ylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

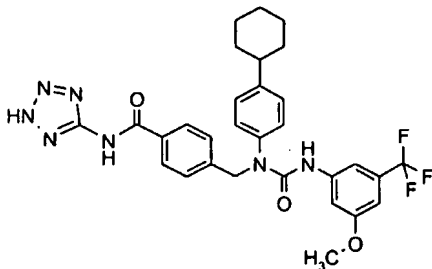
^1H NMR (DMSO- d_6): δ 1.5-1.6 (6H, m), 3.15 (4H, bs), 4.93 (2H, s), 6.94 (2H, d), 7.10 (2H, d), 7.22 (2H, d), 7.45 (2H, d), 7.55 (2H, d), 8.03 (2H, d), 8.10 (1H, s), 12.4 (1H, s).

HPLC-MS (Method B): m/z = 581 (M+1), R_t = 5.02 min.

10

EXAMPLE 319 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



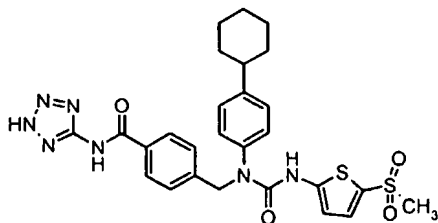
15

^1H NMR (DMSO- d_6): δ 12.40 (br s, 1H); 8.60 (s, 1H); 8.05 (d, 2H); 7.52 (s, 1H); 7.48 (s, 1H); 7.46 (d, 2H); 7.20 (dd, 4H); 6.80 (s, 1H); 5.03 (s, 2H); 3.78 (s, 3H); 1.85-1.60 (m, 5H); 1.50-1.15 (m, 5H).

20 HPLC-MS (Method B): m/z = 594 (M+1). R_t = 7.92 min.

EXAMPLE 320 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(5-methylsulfonylthiophen-2-yl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

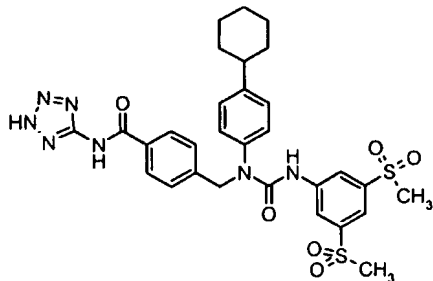
^1H NMR (DMSO- d_6): δ 12.40 (s, 1H); 10.10 (s, 1H); 8.06 (d, 2H); 7.42 (m, 3H); 7.28 (d, 2H); 7.19 (d, 2H); 6.70 (d, 1H); 3.20 (s, 3H); 1.75-1.60 (m, 5H); 1.50-1.10 (m, 5H).

HPLC-MS (Method B): m/z = 580 ($M+1$). R_t = 6.45 min.

10

EXAMPLE 321 (general procedure (L))

4-[3-(3,5-Bis(methylsulfonyl)phenyl)-1-(4-cyclohexylphenyl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



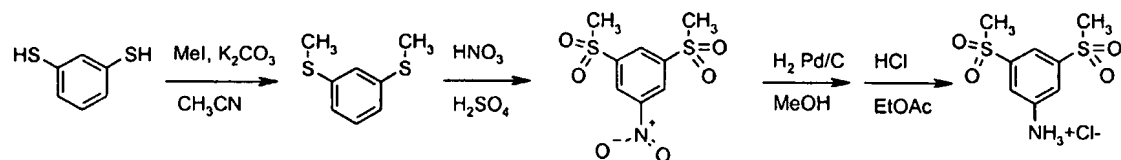
15

^1H NMR (DMSO- d_6): δ 8.45 (s, 2H); 8.05-7.95 (m, 3H); 7.50-7.42 (m, 2H); 7.22 (dd, 4H); 5.00 (s, 2H); 1.90-1.70 (m, 5H); 1.45-1.30 (m, 5H).

HPLC-MS (Method B): m/z = 652 ($M+1$). R_t = 6.33 min.

20

Preparation of 3,5-bis(methylsulfonyl)phenylamine:



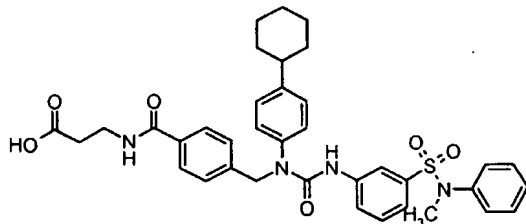
1,3-Bis-benzenethiol (5 g, 35.2 mmol) was dissolved in acetonitrile (50 mL) and added iodo-
methane (4.62 mL, 73.9 mmol) and potassium carbonate (10.7 g, 77.4 mmol). Upon stirring
5 overnight at 25°C, the mixture was filtered and the solvent removed *in vacuo*. The residue
was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was
extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried with
MgSO₄ and evaporated. The residue was distilled at 17 torr, 138°C affording 1,3-
bis(methylsulfonyl)benzene (3.20 g).

10 The above 1,3-bis(methylsulfonyl)benzene (3.20 g) was dissolved in H₂SO₄ (8 mL) and
cooled on an ice bath. A mixture of H₂SO₄ and HNO₃ (1:1, 10 mL) was added dropwise.
Upon stirring 30 min at 25°C, the temperature was raised to 100°C and kept there for 3
hours. Pouring the reaction mixture onto ice (100 mL) afforded a precipitate that still con-
15 tained starting material (2.90 g). This material was dissolved in H₂SO₄ (5.2 mL) and added a
mixture of H₂SO₄ and HNO₃ (1:1, 10.4 mL). The mixture was heated at 110°C overnight and
poured onto ice (100 mL). The formed precipitate was collected by filtration (1.01 g). Chro-
matography on silica gel using a mixture of heptane and ethyl acetate (4:1) as eluent af-
forded the desired 1,3-bis(methylsulfonyl)-5-nitrobenzene (0.7 g).

20 To a slurry of 1,3-bis(methylsulfonyl)-5-nitrobenzene (0.7 g) in methanol (10 mL) was added
palladium on charcoal (0.1 g) and the mixture was hydrogenated at atmospheric pressure
and 25°C for 1 hour. The reaction mixture was filtered and evaporated. The residue was sus-
pended in ethyl acetate (25 mL) and HCl in ethyl acetate (5 mL, appr. 2M) was added. Filtra-
25 tion afforded the desired aniline as its hydrochloride salt, which was converted into an isocy-
anate using diphosgene as described previously.

EXAMPLE 322 (general procedure (L))

3-(4-(1-(4-Cyclohexylphenyl)-3-[3-(methylphenylsulfamoyl)phenyl]ureidomethyl)-benzoyl-amino)propionic acid

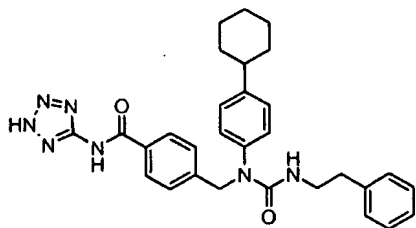


5

HPLC-MS (Method B): m/z = 669 ($M+1$). R_t = 7.38 min.

EXAMPLE 323 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-phenethylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10

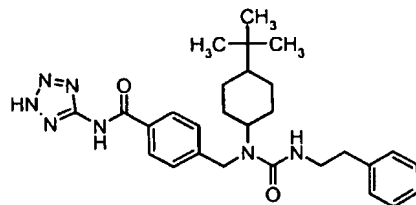
^1H NMR (DMSO): δ 12.40 (s, 1H); 8.00 (d, 2H); 7.40-7.08 (m, 8H); 7.02 (d, 2H); 5.70 (t, 1H); 4.90 (s, 2H); 3.27 (q, 2H); 2.72 (t, 2H); 1.75-1.62 (m, 5H); 1.45-1.10 (m, 5H)

HPLC-MS (Method B): m/z = 524 ($M+1$). R_t = 7.35 min.

15

EXAMPLE 324 (general procedure (L))

4-[1-(4-*tert*-Butylcyclohexyl)-3-phenethylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



^1H NMR (DMSO): δ 12.35 (s, 1H); 8.00 (d, 2H); 7.45-7.10 (m, 7H); 6.45 (s br 1H); 4.50 (d br 2H); 4.10+3.85 (s br, 1H); 3.30 (s br, 2H); 2.80 (s br, 2H); 1.80-1.00 (m, 9H); 0.80 (s, 9H).

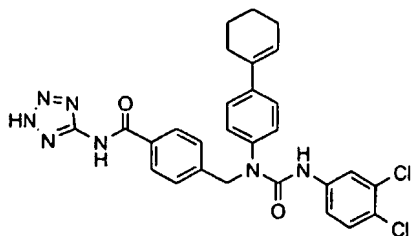
20

HPLC-MS (Method B): m/z = 504 ($M+1$). R_t = 7.05 min.

EXAMPLE 325 (general procedure (L))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-

5 benzamide

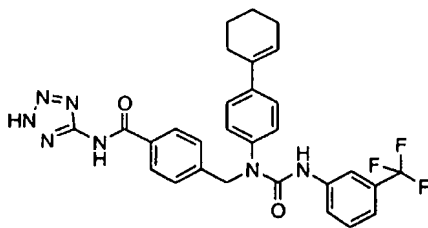


^1H NMR (DMSO): δ 12.30 (s, 1H); 8.52 (s, 1H); 8.05 (d, 2H); 7.70 (s, 1H); 7.50-7.38 (m, 6H);
7.20 (d, 2H); 6.18 (s br, 1H); 5.00 (s, 2H); 2.38 (m, 2H); 2.15 (m, 2H); 1.71 (m, 2H); 1.58 (m,
10 2H).

HPLC-MS (Method B): m/z = 562 ($M+1$). R_t = 7.90 min.

EXAMPLE 326 (general procedure (L))

15 4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-
benzamide

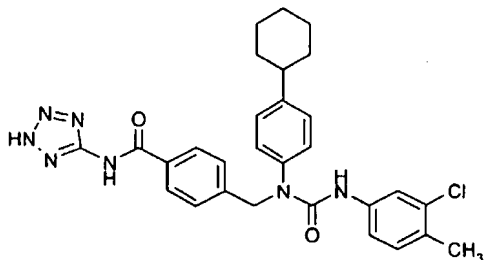


^1H NMR (DMSO): δ 12.35 (s, 1H); 8.60 (s, 1H); 8.05 (2H); 7.91 (s, 1H); 7.78 (d, 1H); 7.48-
20 7.40 (m, 5H); 7.30 (d, 1H); 7.23 (d, 2H); 6.20 (t, 1H); 5.00 (s, 1H); 2.38 (m, 2H); 2.15 (m, 2H);
1.72 (m, 2H); 1.60 (m, 2H).

HPLC-MS (Method B): m/z = 562 ($M+1$). R_t = 7.73 min.

EXAMPLE 327 (general procedure (L))

4-[3-(3-Chloro-4-methylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

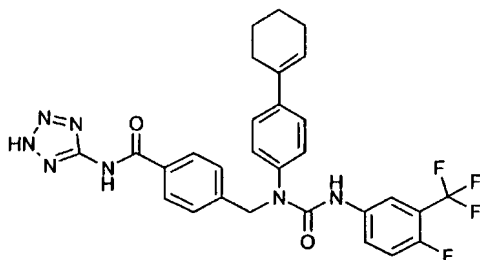
HPLC-MS (method B): m/z: 544, R_t = 7.88 min.

^1H NMR (DMSO-d_6): δ 1.18-1.48 (5H, m), 1.66-1.87 (5H, m), 2.26 (3H, s), 5.00 (2H, s), 7.22 (4H, dd), 7.3 (2H, d), 7.47 (2H, d), 7.62 (1H, s), 8.02 (2H, d), 8.30 (1H, s), 12.2 (1H, broad).

10

EXAMPLE 328 (general procedure (L))

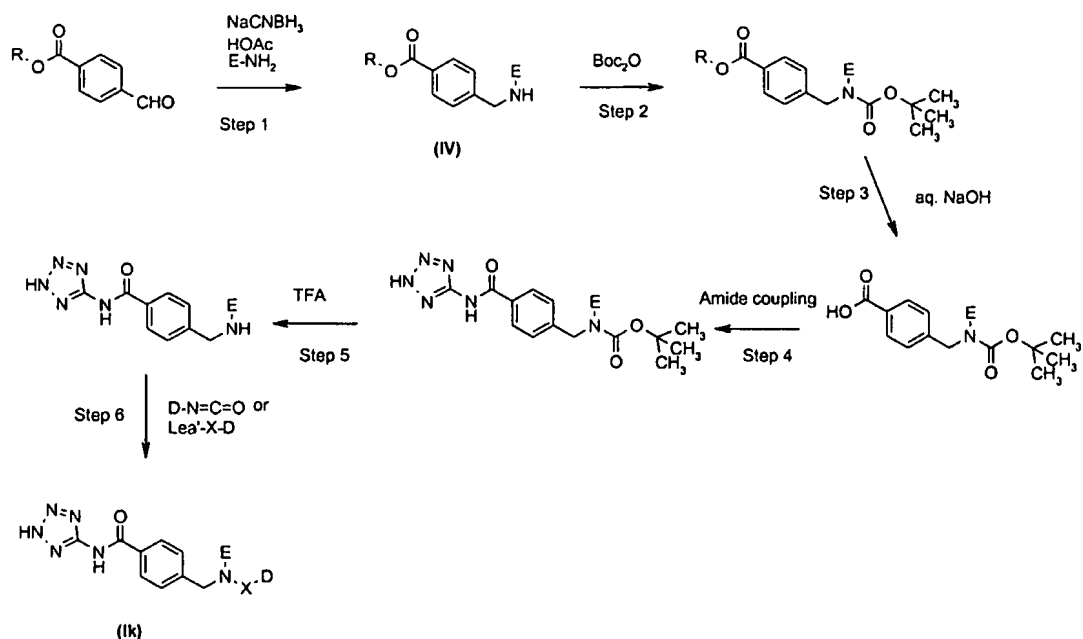
4-[1-(4-Cyclohex-1-enylphenyl)-3-(4-fluoro-3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

HPLC-MS (method B): m/z: 580, R_t = 7.67 min.

General procedure (M) for the solution phase synthesis of compounds of general formula (Ik):



5

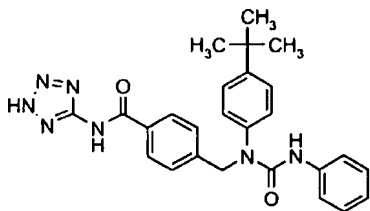
wherein R is C_{1-6} -alkyl,

X, D, and E are as defined in general formula (I), and

10 Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these can either be performed by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

15

EXAMPLE 329 (general procedure (M))4-[1-(4-*tert*-Butylphenyl)-3-phenylureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide5 Step 1:

Step 1 is the same as described in general procedure (K). Alternatively, it can be performed as described for step A of the general procedure (F).

Step 2:

- 10 4-[(4-*tert*-Butylphenylamino)methyl]benzoic acid methyl ester (18.3 g, 61 mmol, prepared as described above) was dissolved in THF (300 mL) and *N,N*-diisopropylethylamine (15 mL, 3.13 mmol), a catalytic amount of 4-dimethylaminopyridine, and di-*tert*-butyldicarbonate (14.8 g, 68 mmol) was added. The resulting mixture was refluxed for 16 hours, cooled and concentrated in vacuo.

15

Step 3:

- The residue was dissolved in ethanol (450 mL) and added 4N aqueous sodium hydroxide (135 mL) and the mixture was stirred at room temperature for 3 days. 4N Hydrochloric acid (140 mL) was added with occasional cooling by addition of crushed ice. The mixture was filtered and the solid was washed with water and dried in vacuo at 30°C to afford 14.5 g (62%) of 4-[[*tert*-butoxycarbonyl-(4-*tert*-butylphenyl)amino]methyl]benzoic acid as a solid.

20

¹H NMR (CDCl₃): δ 1.29 (9H, s), 1.42 (9H, s), 4.89 (2H, s), 7.10 (2H, bd), 7.28 (2H, d), 7.37 (2H, d), 8.05 (2H, d).

25

HPLC-MS (Method B): R_t = 8.10 min, m/z = 328 ((M-^tBu)+1) (trace: 384 (M+1)).

Step 4:

- 30 The above benzoic acid (2.80 g, 7.3 mmol) was dissolved in DMF (20 mL) and 1-hydroxy-benzotriazol (1.18 g, 8.8 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (1.54 g, 8.0 mmol) were added and the resulting mixture was stirred at room tem-

perature for 1 hour. 5-Aminotetrazole hydrate (0.90 g, 8.8 mmol) was added and the mixture was stirred at room temperature for 16 hours. Water (75 mL) was added and the mixture was extracted with ethyl acetate (2 x 75 mL). The combined organic phases were washed with a mixture of water and saturated aqueous sodium chloride (1:1, 2 x 100 mL) and water (100 mL), dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from diethyl ether (30 mL) to afford 1.89 g (57%) of (4-*tert*-butylphenyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid *tert*-butyl ester as a solid.

¹H NMR (CDCl₃): δ 1.29 (9H, s), 1.43 (9H, s), 4.93 (2H, s), 7.13 (2H, bd), 7.30 (2H, d), 8.28 (2H, d), 12.5 (1H, s).

HPLC-MS (Method B): R_t = 7.63 min, m/z = 395 ((M-^tBu)+1) (trace: 451 (M+1)).

Step 5:

The above carbamic acid *tert*-butyl ester (1.7 g, 3.77 mmol) was suspended in ethyl acetate (12 mL) and a 3.4 M dry HCl solution in ethyl acetate (12 mL) was added and the suspension was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and re-suspended in ethyl acetate. Concentration in vacuo afforded 1.49 g (100%) of 4-[(4-*tert*-butylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide hydrochloride as a solid.

¹H NMR (DMSO-*d*₆): δ 1.37 (9H, s), 4.56 (2H, s), 7.18 (2H, bd), 7.38 (2H, d), 7.68 (2H, d), 8.19 (2H, d), 12.4 (1H, s).

HPLC-MS (Method B): R_t = 5.22 min, m/z = 351 (M + 1).

Step 6:

The above benzamide hydrochloride (242 mg, 0.63 mmol) was mixed with dichloromethane (10 mL), *N,N*-diisopropylethylamine (330 μL, 1.89 mmol), and phenylisocyanate (68 μL, 0.63 mmol) and the resulting mixture was stirred at 25°C for 16 hours. Alternatively, Lea'-X-D can be used in which case a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate has to be added. The mixture was diluted with dichloromethane (20 mL) and the mixture was washed with saturated aqueous citric acid (20 mL), the organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from diethyl ether to afford 141 mg (48%) of the title compound as a solid.

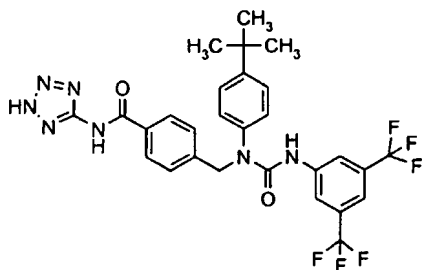
¹H NMR (DMSO-*d*₆): δ 1.29 (9H, s), 5.00 (2H, s), 6.95 (1H, t), 7.2-7.3 (4H, m), 7.3-7.5 (7H, m), 8.04 (2H, d), 8.18 (1H, s), 12.3 (1H, s).

- 5 HPLC-MS (Method B): *R*_t = 7.22 min, *m/z* = 470 (*M* + 1).

Similarly, the following compounds were made.

EXAMPLE 330 (general procedure (M))

- 10 4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

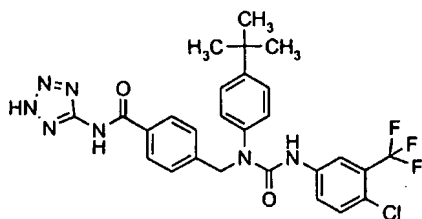


- 15 ¹H NMR (DMSO-*d*₆): δ 1.29 (9H, s), 5.01 (2H, s), 7.30 (1H, t), 7.43 (2H, d), 7.47 (2H, d), 7.64 (1H, s), 8.05 (2H, d), 8.25 (2H, s), 9.00 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B): *R*_t = 8.43 min, *m/z* = 606 (*M* + 1).

EXAMPLE 331 (general procedure (M))

- 20 4-[1-(4-*tert*-Butylphenyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

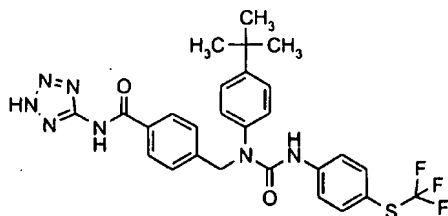


- 25 ¹H NMR (DMSO-*d*₆): δ 1.28 (9H, s), 5.01 (2H, s), 7.23 (2H, d), 7.40 (2H, d), 7.45 (2H, d), 7.56 (1H, d), 7.80 (1H, dd), 8.05 (3H, m), 8.73 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B): $R_t = 8.18$ min, $m/z = 572$ ($M + 1$).

EXAMPLE 332 (general procedure (M))

4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

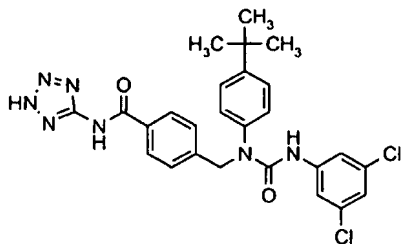


^1H NMR ($\text{DMSO-}d_6$): δ 1.28 (9H, s), 5.02 (2H, s), 7.21 (2H, d), 7.38 (2H, d), 7.46 (2H, d), 7.56 (2H, d), 7.63 (2H, d), 8.04 (2H, d), 8.64 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B): $R_t = 8.20$ min, $m/z = 570$ ($M + 1$).

EXAMPLE 333 (general procedure (M))

4-[1-(4-*tert*-Butylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

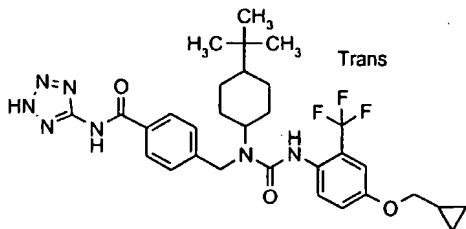


^1H NMR ($\text{DMSO-}d_6$): δ 1.35 (9H, s), 4.95 (2H, s), 6.88 (1H, s), 6.96 (1H, t), 7.10 (2H, d), 7.38 (2H, d), 7.43 (4H, m), 8.13 (2H, d), 8.64 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B): $R_t = 7.98$ min, $m/z = 538$ ($M + 1$).

EXAMPLE 334 (general procedure (M))

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxy-2-trifluoromethylphenyl)ureido-methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



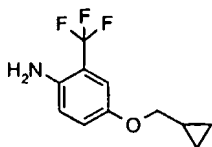
5

¹H NMR (DMSO-*d*₆): δ 7.98 (3H, m), 7.42 (2H, d), 7.32 (1H, d), 7.18 (1H, d), 7.13 (1H, s), 4.55 (2H, broad), 3.88 (2H, d), 1.80-0.85 (10H, m), 0.80 (9H, s), 0.60 (2H, m), 0.33 (2H, m).

HPLC-MS (method B): *m/z*: 614, *R*_t = 8.32 min.

10

Synthesis of intermediate 4-cyclopropylmethoxy-2-trifluoromethylphenylamine:



15 1-Nitro-4-hydroxy-2-trifluoromethylbenzene (5.0 g, 14 mmol) and cyclopropylcarbinol (1.75 g, 24 mmol) were dissolved in THF (20 mL) under nitrogen. Triphenylphosphine (9.5 g, 36 mmol) was added and diethyl azodicarboxylate (5.7 mL, 36 mmol) dissolved in THF (10 mL) was added over 30 minutes. The reaction mixture was stirred at 20°C for 16 hours and then concentrated in vacuo. The residue was dissolved in ethyl acetate (25 mL) and heptane (40 mL). The mixture was filtered and the filtrate was concentrated in vacuo. The residue was
20 purified by flash chromatography (350 g silica) using heptane and ethyl acetate (9:1) as eluent to give 1.4 g of 4-cyclopropylmethoxy-1-nitro-2-trifluoromethylbenzene.

HPLC-MS (method B): *m/z*: 262, *R*_t = 7.6 min.

25 Stannous chloride (4.75 g, 21 mmol) was added to a solution of 4-cyclopropylmethoxy-1-nitro-2-trifluoromethylbenzene (1.1 g, 4.2 mmol) in ethanol (12 mL). The reaction temperature was raised to 70°C for 1.5 hour. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (20 mL). Water (15 mL) was added and sodium hydrogen

carbonate was added until pH 7. The mixture was filtered and the organic phase collected. The aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (38 g) using heptane and ethyl acetate (9:1) as eluent to give 0.49 g of 4-cyclopropylmethoxy-2-trifluoromethylphenylamine.

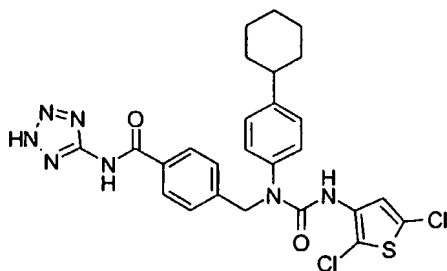
¹H NMR (DMSO-*d*₆): δ 6.98 (1H, d), 6.85 (1H, s), 6.79 (1H, d), 5.10 (2H, broad), 3.72 (2H, d), 1.15 (1H, m), 0.53 (2H, m), 0.31 (2H, m).

HPLC-MS (method B): *m/z*: 232, *R*_t = 5.9 min.

This intermediate product was transformed to the corresponding phenylcarbamate using the same methodology as described in example 239 and used for the synthesis of the title compound.

EXAMPLE 335 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(2,5-dichlorothiophen-3-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



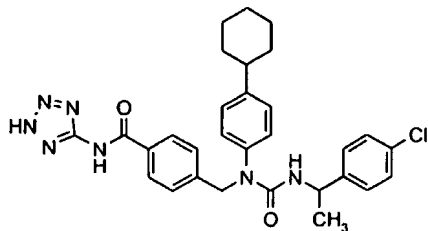
The intermediate 2,5-dichloro-3-thienylisocyanate was prepared by a Curtius reaction on 2,5-dichloro-3-thienylcarboxylic acid.

¹H NMR (DMSO-*d*₆): δ 7.63 (s, 1H), 7.49 (d, 2H), 7.33 (d, 2H), 7.27 (s, 1H), 7.22 (dd, 4H), 4.88 (s, 2H), 1.8-1.6 (m, 5H), 1.4-1.2 (m, 6H)

HPLC-MS (method B): *m/z*: 567, *R*_t = 8.5 min.

EXAMPLE 336 (general procedure (M))

4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

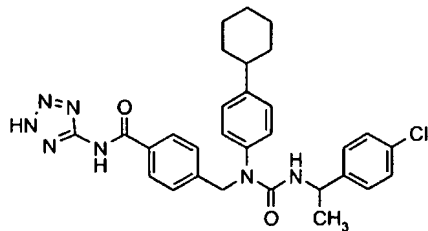
HPLC-MS (Method B): m/z = 558 ($M+1$), R_t = 7.83 min.

^1H NMR ($\text{DMSO}-d_6$): δ 1.2 – 1.4 (8H, m), 1.7 – 1.8 (5H, m), 4.90 (3H, m), 7.1 – 7.2 (4H, m), 7.35 (5H, m), 7.52 (1H, m), 8.02 (2H, d).

10

EXAMPLE 337 (general procedure (M))

4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide, enantiomer A, first eluted



15

The compound of example 336 was separated into pure enantiomers using a (*R,R*)-Whelk-O 1 column (250-21.1 mm, Regis) eluted with n-heptane:ethanol, 1:1 at a flow rate of 15 mL/min. The compound was dissolved in ethyl acetate:ethanol:acetic acid:n-heptane (0.9:1.1:0.09:1.1), 5 mg/ml, injected in portions of 10 mg (2 ml) and detected at 225 and 254 nm. The two enantiomers A and B eluted at T_R 9-12 min (A) and T_R 37-42 min (B), respectively, and the fractions were collected (10 mL/fraction) and pooled. The purity of the enantiomers was determined using a Chiralcel OD (250-4.6mm, Daicel) column eluted with ethanol:(n-heptane+0.1% TFA), 40:60 at a flow rate of 0.6 mL/min, T_R (A): 14.6 min and T_R (B): 12.0 min.

25

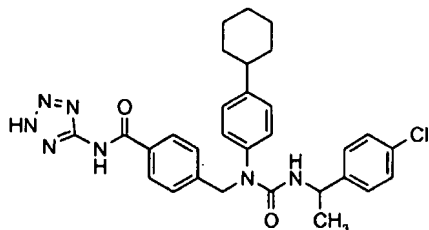
Used instruments:

HP1090 (analytical runs), Gilson HPLC system (preparative runs).

EXAMPLE 338 (general procedure (M))

4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-

5 benzamide, enantiomer B, second eluted

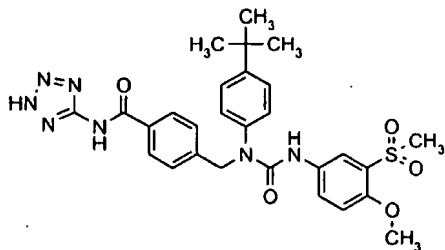


This compound was obtained as the second eluting enantiomer (enantiomer B) of example 337. For HPLC-data, see example 337.

10

EXAMPLE 339 (general procedure (M))

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonyl-4-methoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

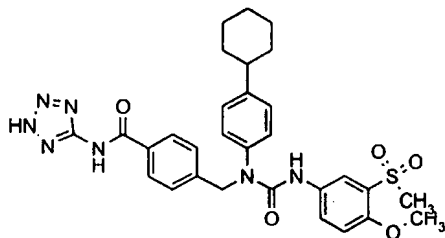
4-Methoxy-3-methylsulfonylaniline was prepared as described in Holmes, Ingold & Ingold, J. Chem. Soc., 1927, 1684-90, and the corresponding isocyanate was prepared using the triphosgene method described in example 240.

20 ¹H NMR (DMSO-*d*₆): δ 1.30 (9H, s), 3.22 (3H, s), 3.90 (3H, s), 5.00 (2H, s), 7.2 (3H, m), 7.40 (2H, d), 7.45 (2H, d), 7.80 (1H, dd), 7.94 (1H, d), 8.03 (2, d), 8.48 (1H, s), 12.2 (H, s).

HPLC-MS (Method B): *m/z* = 578 (*M*+1), *R*_t = 5.63 min.

EXAMPLE 340 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonyl-4-methoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



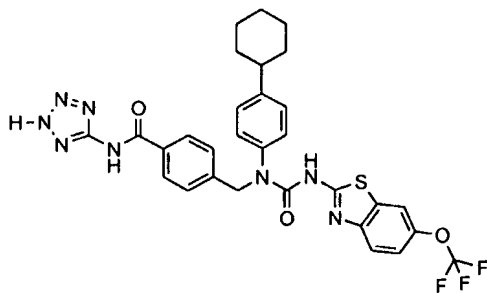
5

¹H NMR (DMSO-*d*₆): δ 1.2-1.4 (5H, m), 1.55-1.8 (5H, m), 3.22 (3H, s), 3.90 (3H, s), 4.99 (2H, s), 7.2 (5H, m), 7.44 (2H, d), 7.79 (1H, dd), 7.92 (1H, d), 8.02 (2H, d), 8.47 (1H, s), 11.9 (1H, s), 12.3 (1H, s).

10 HPLC-MS (Method B): *m/z* = 604 (*M*+1), *R*_t = 6.40 min.

EXAMPLE 341 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(6-trifluoromethoxybenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

Using isocyanate formed in situ from (substituted) 2-aminobenzothiazole and diphosgene in pyridine:

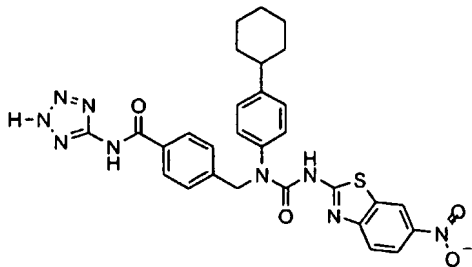
2-Amino-6-(trifluoromethoxy)benzothiazole (334 mg, 1.43 mmol) was dissolved in pyridine (5 mL). Diphosgene (0.1 mL, 0.83 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide (400 mg, 1.06 mmol) was added and the reaction mixture was heated to 80°C for two hours. The reaction mixture was poured into acetonitrile (50 mL) and stored at -20°C overnight and the resulting precipitate was subsequently collected by filtration to afford the title compound.

25

HPLC-MS (Method D): $R_t = 6.20$ min, $m/z = 637$ ($M+1$).

EXAMPLE 342 (general procedure (M))

- 5 4-[1-(4-Cyclohexylphenyl)-3-(6-nitrobenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

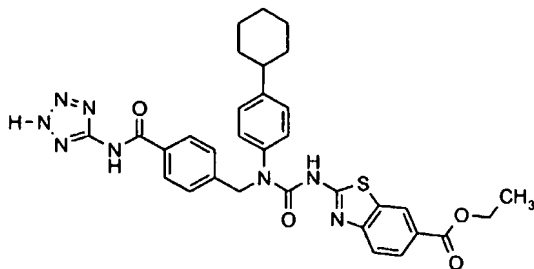


HPLC-MS (Method D): $R_t = 5.67$ min, $m/z = 598$ ($M+1$).

10

EXAMPLE 343 (general procedure (M))

- 10 2-{3-[4-(4-Cyclohexylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]ureido]benzothiazole-6-carboxylic acid ethyl ester

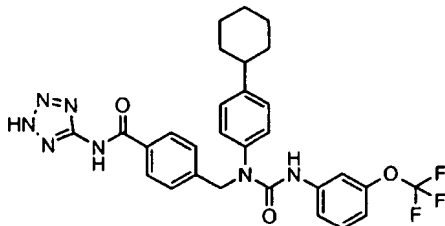


15

HPLC-MS (Method D): $R_t = 5.83$ min, $m/z = 625$ ($M+1$).

EXAMPLE 344 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

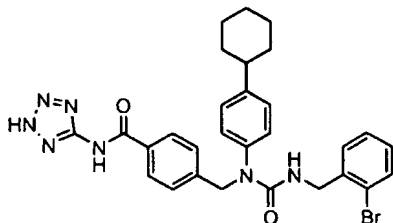
^1H NMR (DMSO- d_6): δ 1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 5.00 (s, 2H), 6.93 (d, 1H), 7.22 (m, 4H), 7.34 (t, 1H), 7.45 (m, 3H), 7.60 (s, 1H), 8.05 (d, 2H), 8.53 (s, 1H), 12.4 (bs, 1H).

HPLC-MS (method B): R_t = 7.93 min, m/z = 580 ($M + 1$).

10

EXAMPLE 345 (general procedure (M))

4-[3-(2-Bromobenzyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



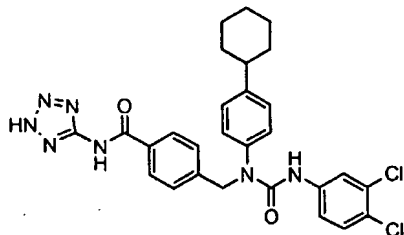
15

^1H NMR (DMSO- d_6): δ 1.2-1.5 (m, 5H), 1.7-1.8 (m, 5H), 4.25 (d, 2H), 4.92 (s, 2H), 6.46 (m, 1H), 7.15-7.30 (m, 6H), 7.45 (m, 3H), 7.56 (d, 1H), 8.07 (d, 2H), 12.4 (s, 1H).

EXAMPLE 346 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

20



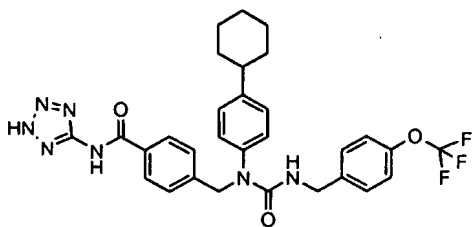
¹H NMR (DMSO-*d*₆): δ 1.3-1.4 (m, 5H), 1.7-1.8 (m, 5H), 5.00 (s, 2H), 7.22 (m, 4H), 7.45 (m, 3H), 7.83 (s, 1H), 8.04 (d, 2H), 8.53 (s, 1H), 12.4 (s, 1H).

HPLC-MS (method B): R_t = 8.07 min, m/z = 564 (M + 1).

5

EXAMPLE 347 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxybenzyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



10

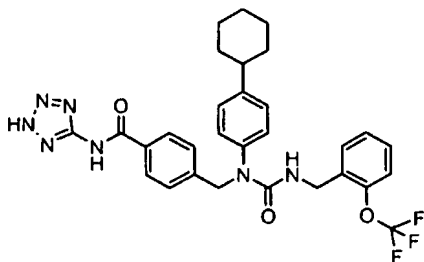
¹H NMR (DMSO-*d*₆): δ 1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 2.57 (s, 1H), 4.28 (d, 2H), 4.91 (s, 2H), 6.57 (t, 1H), 7.14 (d, 2H), 7.22 (d, 2H), 7.29-7.40 (m, 6H), 8.02 (d, 2H), 12.3 (s, 1H).

HPLC-MS (method B): R_t = 7.68 min, m/z = 594 (M + 1).

15

EXAMPLE 348 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(2-trifluoromethoxybenzyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



20

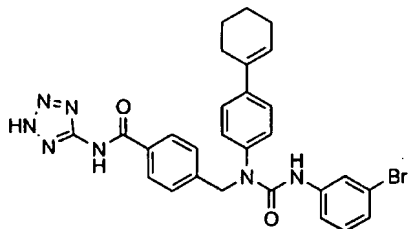
¹H NMR (DMSO-*d*₆): δ 1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 2.55 (s, 1H), 4.34 (d, 2H), 4.91 (s, 2H), 6.44 (t, 1H), 7.17 (d, 2H), 7.22 (d, 2H), 7.29-7.42 (m, 6H), 8.02 (d, 2H), 12.3 (s, 1H).

HPLC-MS (method B): R_t = 7.72 min, m/z = 594 (M + 1).

25

EXAMPLE 349 (general procedure (M))

4-[3-(3-Bromophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



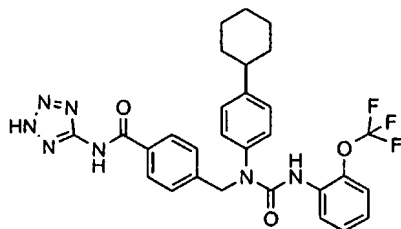
5

^1H NMR (DMSO- d_6): δ 1.59 (m, 2H), 1.72 (m, 2H), 2.17 (m, 2H), 2.35 (m, 2H), 5.01 (s, 2H), 6.19 (t, 1H), 7.1-7.25 (m, 4H), 7.5-7.5 (m, 5H), 7.79 (s, 1H), 8.04 (d, 2H), 8.42 (s, 1H), 12.4 (s, 1H).

10 HPLC-MS (method C): R_t = 5.73 min, m/z = 574 ($M + 1$).

EXAMPLE 350 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(2-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



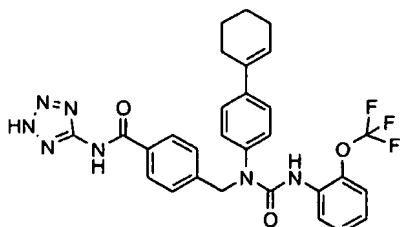
15

^1H NMR (DMSO- d_6): δ 1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 4.99 (s, 2H), 6.44 (t, 1H), 7.12 (t, 1H), 7.20 (s, 1H), 7.25-7.35 (m, 6H), 7.49 (d, 2H), 8.05 (d, 2H), 8.11 (d, 1H), 12.4 (s, 1H).

20 HPLC-MS (method B): R_t = 8.20 min, m/z = 580 ($M + 1$).

EXAMPLE 351 (general procedure (M))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(2-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



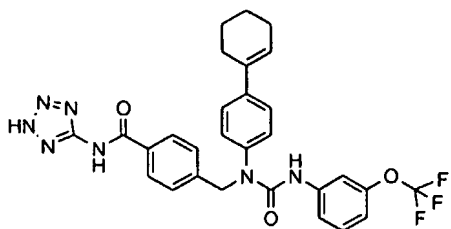
5

^1H NMR (DMSO- d_6): δ 1.60 (m, 2H), 1.71 (m, 2H), 2.17 (m, 2H), 2.33 (m, 2H), 5.01 (s, 2H), 6.19 (m, 1H), 7.15 (t, 1H), 7.30-7.50 (m, 9H), 7.99 (d, 1H), 8.05 (d, 2H), 12.4 (s, 1H).

10 HPLC-MS (method B): R_t = 7.90 min, m/z = 578 (M + 1).

EXAMPLE 352 (general procedure (M))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

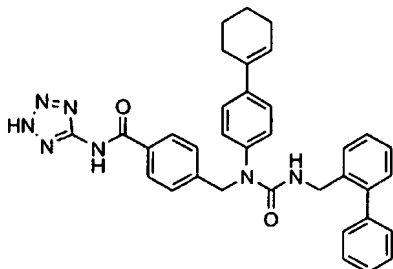


15

^1H NMR (DMSO- d_6): δ 1.60 (m, 2H), 1.70 (m, 2H), 2.18 (m, 2H), 2.34 (m, 2H), 5.00 (s, 2H), 6.19 (t, 1H), 6.93 (d, 1H), 7.22 (d, 2H), 7.35 (t, 1H), 7.4-7.5 (m, 5H), 7.60 (s, 1H), 8.03 (d, 2H), 8.53 (s, 1H), 12.4 (s, 1H).

20

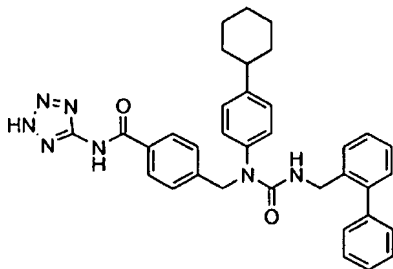
HPLC-MS (method B): m/z = 578 (M + 1), R_t = 7.77 min.

EXAMPLE 353 (general procedure (M))4-[3-Biphenyl-2-ylmethyl-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

5

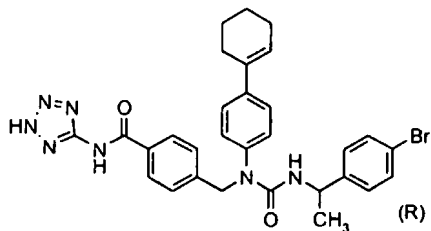
¹H NMR (DMSO-*d*₆): δ 1.59 (m, 2H), 1.70 (m, 2H), 2.15 (m, 2H), 2.33 (m, 2H), 4.21 (d, 2H), 4.90 (s, 2H), 6.15 (t, 1H), 6.28 (t, 1H), 7.10 (d, 2H), 7.18 (d, 1H), 7.3-7.5 (m, 15H), 7.95 (s, 1H), 8.00 (d, 2H), 12.3 (s, 1H).

10 HPLC-MS (method B): R_t = 7.78 min, m/z = 584 (M + 1).

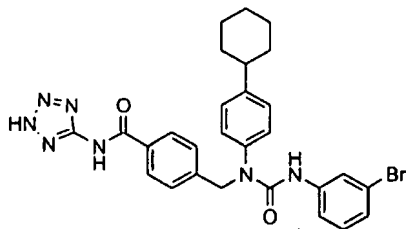
EXAMPLE 354 (general procedure (M))4-[3-Biphenyl-2-ylmethyl-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

15

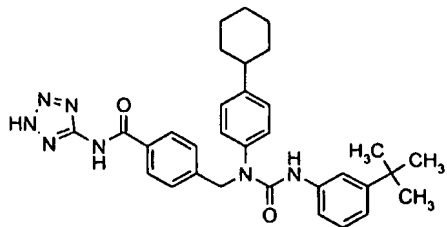
¹H NMR (DMSO-*d*₆): δ 1.15-1.4 (m, 5H), 1.6-1.8 (m, 5H), 4.20 (d, 2H), 4.88 (s, 2H), 6.16 (t, 1H), 7.08 (d, 2H), 7.11 (m, 3H), 7.3-7.45 (m, 11H), 8.00 (d, 2H), 12.4 (s, 1H).

EXAMPLE 355 (general procedure (M))(R)-4-[3-[1-(4-Bromophenyl)ethyl]-1-(cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

5

HPLC-MS (method B): $R_t = 7.72$ min, $m/z = 601$ ($M + 1$).EXAMPLE 356 (general procedure (M))4-[3-(3-Bromophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

10

 ^1H NMR ($\text{DMSO}-d_6$): δ 1.3-1.5 (m, 5H), 1.7-1.8 (m, 5H), 4.99 (s, 2H), 7.1-7.2 (m, 7H), 7.4-7.5 (m, 3H), 7.78 (s, 1H), 8.02 (d, 2H), 8.40 (s, 1H), 12.4 (s, 1H).15 HPLC-MS (method B): $m/z = 576$ ($M + 1$), $R_t = 7.88$ min.EXAMPLE 357 (general procedure (M))4-[1-(4-Cyclohexylphenyl)-3-(3-*tert*-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

20

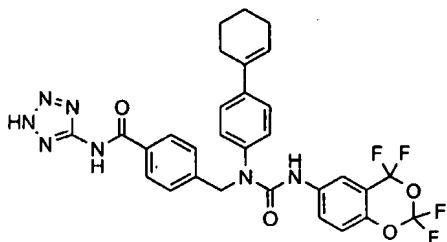
¹H NMR (DMSO-*d*₆): δ 1.25 (s, 9H), 1.3-1.5 (m, 5H), 1.7-1.8 (m, 5H), 4.99 (s, 2H), 6.99 (d, 1H), 7.1-7.3 (m, 6H), 7.4-7.5 (m, 3H), 8.05 (d, 2H), 8.13 (s, 1H), 12.4 (s, 1H).

HPLC-MS (method C): *m/z* = 552 (*M* + 1), *R*_t = 6.27 min.

5

EXAMPLE 358 (general procedure (M))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



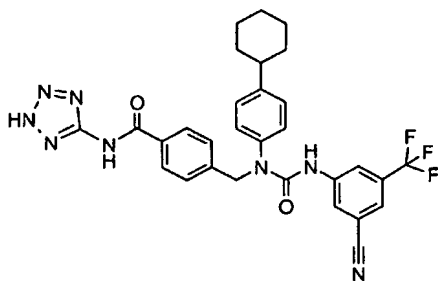
10

¹H NMR (DMSO-*d*₆): δ 1.60 (2H, m), 1.70 (2H, m), 2.17 (2H, br s), 2.35 (2H, br s), 5.03 (2H, s), 6.20 (1H, s), 7.20-7.30 (2H, m), 7.35-7.50 (6H, m), 7.85, (1H, d), 8.04 (3H, m), 8.65, (1H, s), 12.40 (1H, s).

15

EXAMPLE 359 (general procedure (M))

4-[3-(3-Cyano-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



20

¹H NMR (DMSO): δ 12.40 (s, 1H); 8.90 (s, 1H); 8.25 (s, 1H); 8.20 (s, 1H); 8.02 (d, 2H); 7.86 (s, 1H); 7.48 (d, 2H); 7.22 (s, 4H); 5.00 (s, 2H); 1.85-1.65 (m, 5H); 1.45-1.20 (m, 5H).

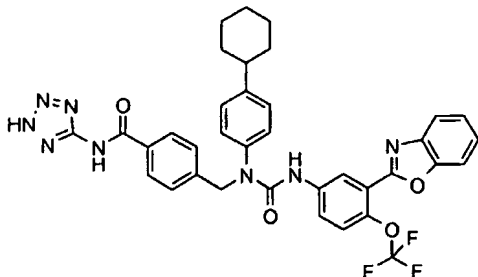
HPLC-MS (Method B): *m/z* = 589 (*M*+1). *R*_t = 5.83 min.

25

Preparation of 3-Amino-5-trifluoromethylbenzonitrile:

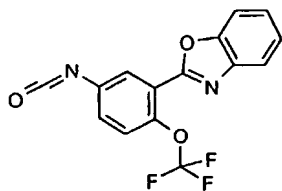
- Commercially available 3-nitro-5-trifluoromethylbenzoic acid (10 g, 42.5 mmol) was dissolved in toluene (50 mL) and DMF (0.5 mL) and added thionyl chloride (5 mL). The mixture was refluxed for 4 hours. After cooling to 20°C, the volatiles were removed in vacuo. The residue
- 5 was re-dissolved in toluene (50 mL) and stripped. Toluene (50 mL) was added to the residue, and the solution was cooled on ice and added concentrated aqueous ammonia (10 mL). The mixture was stirred overnight and allowed to reach 20°C. 3-Nitro-5-trifluoromethylbenzamide was collected by filtration.
- 10 The above 3-nitro-5-trifluoromethylbenzamide (7.25 g) was dissolved in DMF (25 mL) and added to an ice-cooled solution of POCl₃ (10 mL) in DMF (20 mL). The mixture was stirred 30 min at 0°C and then heated to 40°C for 4 hours. The reaction mixture was added to ice (300 mL), stirred for 1 hour and 3-nitro-5-trifluoromethylbenzonitrile was collected by filtration.
- 15 3-Nitro-5-trifluoromethylbenzonitrile (1 g, 4.63 mmol) was dissolved in methanol (8 mL) and added activated charcoal (0.1 g), FeCl₃·6H₂O (17 mg, 0.06 mmol) and *N,N*-dimethylhydrazine (3.7 mL, 48.6 mmol). The mixture was refluxed overnight. The mixture was filtered and the volatiles removed in vacuo. The residue was purified by chromatography on silica using a
- 20 mixture of heptane and ethyl acetate (4:1) as eluent affording 3-amino-5-trifluoromethylbenzonitrile.

The aniline was converted into the corresponding isocyanate by methods already described.

EXAMPLE 360 (general procedure (M))4-[3-(3-Benzoxazol-2-yl-4-trifluoromethoxyphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5 ¹H NMR (DMSO-*d*₆): δ 1.32-1.50 (m, 5H); 1.63-1.86 (m, 5H); 5.04 (s, 2H); 7.26 (s, 5H); 7.43-7.55 (m, 5H); 7.76-7.92 (m, 3H); 8.05 (d, 2H); 8.51 (d, 1H); 8.84 (s, 1H); 12.17 (s, 1H).

Preparation of 2-(5-isocyanato-2-trifluoromethoxyphenyl)benzoxazole:



10

Concentrated sulphuric acid (26 mL) was added dropwise to a flask containing 26 mL of 100% nitric acid while the temperature was kept at 2-6°C. Stirring was continued at this temperature while 2-(trifluoromethoxy)benzonitrile (26.16 g, 0.1398 mol) was added dropwise. When the addition was complete, the mixture was heated at 60°C for 1 hour and poured into
 15 ice water. The precipitate was filtered off and treated with aqueous sodium hydrogen carbonate until neutral reaction. The crystals were collected and dried to afford 28.53 g (82%) of 5-nitro-2-trifluoromethoxybenzoic acid.

Mp 134-135°C.

20

¹H NMR (DMSO-*d*₆): δ 7.79 (dd, 1H), 8.53 (dd, 1H), 8.64 (d, 1H), 14.13 (br s, 1H).

A mixture of 5-nitro-2-trifluoromethoxybenzoic acid (6.43 g, 25.6 mmol) and 128 mg of 10% Pd/C in 10 mL of absolute ethanol was stirred in a hydrogen atmosphere overnight at room
 25 temperature. The catalyst was filtered off and the filtrate was evaporated to dryness. The re-

residue was triturated with diethyl ether and the crystals were filtered off and dried to afford 1.644 g (29%) of 5-amino-2-trifluoromethoxybenzoic acid.

Mp 196-197°C.

5

¹H NMR (DMSO-*d*₆): δ 5.83 (br s, 2H), 6.74 (dd, 1H), 7.06 (m, 2H), 12.52 (br s, 1H).

A mixture 750 mg of 5-amino-2-trifluoromethoxybenzoic acid (750 mg, 3.39 mmol) and 2-aminophenol (370 mg, 3.39 mmol) in 10 mL of polyphosphoric acid was heated and stirred at 250°C for 3.5 hours. The mixture was poured into ice water under stirring, followed by addition of NaHCO₃ until pH 8. The mixture was extracted with ethyl acetate. The organic phase was washed with water twice, brine, rinsed with activated charcoal, dried over MgSO₄ and evaporated to give an oil, which contained two compounds, according to TLC. This mixture was dissolved in DMF and separated on semi preparative HPLC (Gilson 215 Liquid Handler), stationary phase: RP18, mobile phase: Water/MeCN gradient 95%/5% - 5%/95% to afford 216mg (22%) of 3-benzoxazol-2-yl-4-trifluoromethoxyphenylamine as crystals.

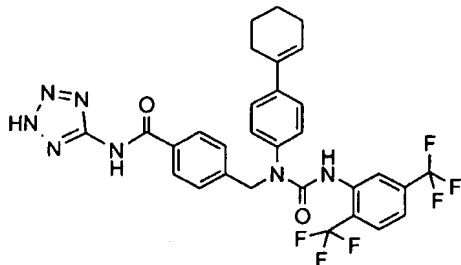
Mp 133-135°C.

¹H NMR (DMSO-*d*₆): δ 5.73 (br s, 2H), 6.82 (dd, 1H), 7.23 (dd, 1H), 7.44 (m, 3H), 7.82 (m, 2H).

A solution of 3-benzoxazol-2-yl-4-trifluoromethoxyphenylamine (210 mg, 0.71 mmol) in 5 mL of dry toluene was stirred while 1.15 mL of 3.1N hydrochloric acid in ethyl acetate was added. The precipitate was concentrated by evaporation. Another 5 mL of toluene was added followed by evaporation. This procedure was repeated 3 times to remove excess of hydrochloric acid. The amine hydrochloride was dissolved in 5 mL of toluene and trichloromethyl chloroformate (0.853 mL, 7.1 mmol) was added. The mixture was refluxed overnight under a nitrogen atmosphere, evaporated at 70°C followed by stripping with dry toluene. 2-(5-Isocyanato-2-trifluoromethoxyphenyl)benzoxazole (160 mg, 70%) was obtained as crystals and used immediately to synthesize the title compound.

EXAMPLE 361 (general procedure (M))

4-[3-(2,5-Bis(trifluoromethyl)phenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

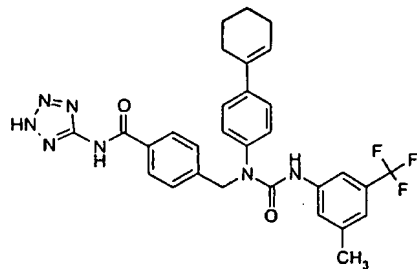
HPLC-MS (method B): m/z : 630, R_t = 8.48 min.

^1H NMR ($\text{DMSO}-d_6$): δ 1.54-1.62 (2H, m), 1.68-1.78 (2H, m), 2.18 (2H, broad), 2.34 (2H, broad), 5.02 (2H, s), 6.21 (1H, broad), 7.32 (2H, d), 7.48 (4H, dd), 7.65 (1H, d), 7.90 (1H, d), 8.02 (2H, d), 8.40 (1H, s), 11.95 (1H, broad).

10

EXAMPLE 362 (general procedure (M))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methyl-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

HPLC-MS (method B): m/z : 576, R_t = 8.02 min.

^1H NMR ($\text{DMSO}-d_6$): δ 1.60 (2H, m), 1.70 (2H, m), 2.17 (2H, m), 2.32 (3H, s), 2.35 (2H, m), 5.02 (2H, s), 6.20 (s, 1H), 7.12 (1H, s), 7.24 (2H, d), 7.42 (2H, d), 7.46 (2H, d), 7.60 (1H, s), 7.74 (1H, s), 8.03 (2H, d), 8.49 (1H, s), 12.39 (1H, s).

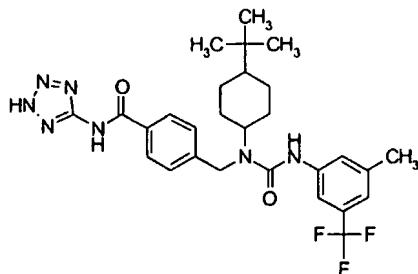
20

Microanalysis: calculated for $\text{C}_{30}\text{H}_{28}\text{F}_3\text{N}_7\text{O}_2$:
62.60% C; 4.90% H; 17.03% N. Found:

62.57% C; 4.95% H; 17.07% N.

EXAMPLE 363 (general procedure (M))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methyl-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-
5 tetrazol-5-yl)benzamide

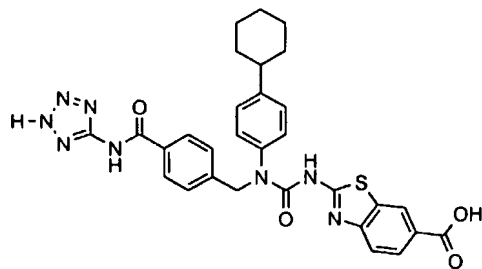


HPLC- MS (method D): m/z : 558, R_t = 5.44 min.

- 10 ^1H NMR ($\text{DMSO}-d_6$): δ 0.83 (9H,s), 0.96 (1H, m), 1.14 (2H,m), 1.44 (2H,m), 1.73 (4H,m), 2.25 (3H, s), 4.04 (1H,m), 4.64 (2H,s), 7.10 (1H,s), 7.40 (2H,d), 7.59 (1H,s), 7.75 (1H,s), 8.03 (2H,d), 8.66 (1H,s), 12.49 (1H,s).

EXAMPLE 364

- 15 2-{3-(4-Cyclohexylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzothiazole-6-carboxylic acid



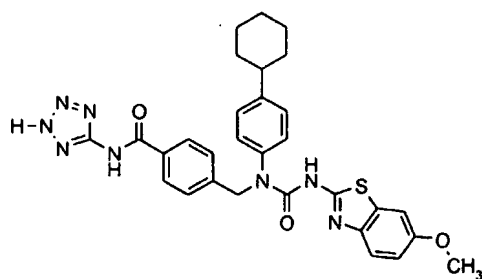
- 20 2-{3-(4-Cyclohexylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzothiazole-6-carboxylic acid ethyl ester (16 mg, 0.025 mmol) was dissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 16 hours. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration to afford the title compound.

HPLC-MS (Method B): $R_t = 6.68$ min, $m/z = 597$ ($M+1$).

EXAMPLE 365 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(6-methoxybenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

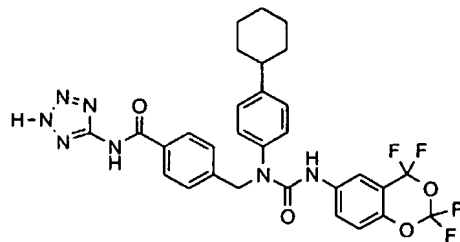
5



HPLC-MS (Method D): $R_t = 5.53$ min, $m/z = 583$ ($M+1$).

10 EXAMPLE 366 (general procedure (M))

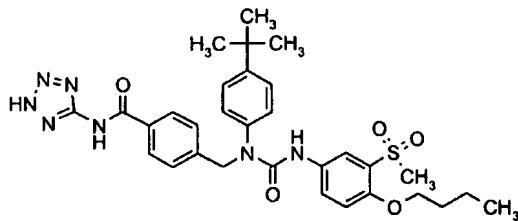
4-[1-(4-Cyclohexylphenyl)-3-(2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxin-6-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15 HPLC-MS (Method D): $R_t = 6.17$ min, $m/z = 626$ ($M+1$).

EXAMPLE 367 (general procedure (M))

4-[3-(4-Butoxy-3-methylsulfonylphenyl)-1-(4-tert-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

4-Butoxy-3-methylsulfonylaniline was prepared from 4-methoxy-3-methylsulfonylaniline as described in Gitis, Malinovskii, Prokhoda & Sribnaya J. Gen. Chem. USSR (Engl. Transl.) 1960 (30), 3045-7, and the corresponding isocyanate was prepared using the triphosgene method described in example 240.

5

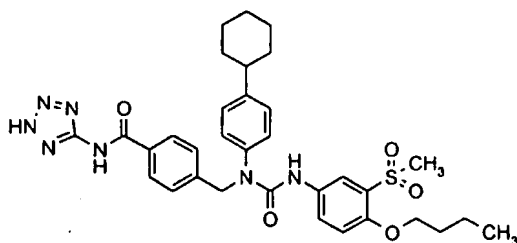
^1H NMR ($\text{DMSO}-d_6$): δ 4.11 (2H, t), 4.96 (2H, s), 7.18 (3H, m), 7.37 (5H, m), 7.9 (3H, m), 8.45 (1H, s).

HPLC-MS (Method B): m/z = 620 ($M+1$), R_t = 6.97 min.

10

EXAMPLE 368 (general procedure (M))

4-[3-(4-Butoxy-3-methylsulfonylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



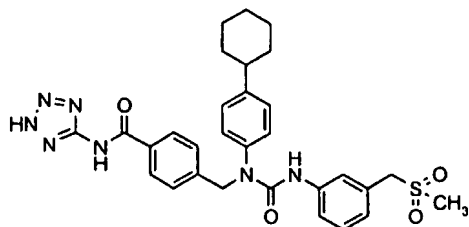
15

^1H NMR ($\text{DMSO}-d_6$): δ 0.94 (3H, t), 1.3-1.55 (8H, m), 1.7-1.8 (8H, m), 3.22 (3H, s), 4.10 (2H, t), 4.98 (2H, s), 7.2-7.3 (5H, m), 7.46 (2H, d), 7.78 (1H, dd), 7.93 (1H, d), 8.05 (2H, d), 8.45 (1H, s), 12.4 (1H, s).

20 HPLC-MS (Method B): m/z = 646 ($M+1$), R_t = 7.70 min.

EXAMPLE 369 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylmethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



25

3-Methylsulfonylmethylphenyl isocyanate was prepared as follows:

m-Nitrobenzyl chloride (4.21 g, 24.5 mmol) was dissolved in DMF (40 mL) and added sodium methanesulfinate (3.00 g, 29.4 mmol) and the resulting mixture was stirred at room temperature for 16 hours. After evaporation of the solvent in vacuo the residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL) and the combined organic phases were dried (MgSO₄) and evaporated in vacuo to afford 4.45 g (84 %) 1-methylsulfonylmethyl-3-nitrobenzene.

¹H NMR (CDCl₃): δ 2.92 (3H, s), 4.39 (2H), 7.65 (1H, t), 7.80 (1H, d), 8.29 (2H, m).

10

1-Methylsulfonylmethyl-3-nitrobenzene (4.70 g, 21.8 mmol) was added ethanol (70 mL) and the mixture was heated to reflux. At reflux the mixture was added SnCl₂ dihydrate (24.6 g, 109 mmol) and heating at reflux was continued for 1 hour. After cooling, the mixture was poured into ice/water (200 mL) and neutralised (to pH 7) with 1 N sodium hydroxide. The mixture was filtered through celite, and the filter cake was washed with ethyl acetate. The phases from the combined filtrate and washings were separated, and the aqueous phase was extracted with ethyl acetate (2 x 150 mL). The combined organic phases were dried (MgSO₄) and evaporated in vacuo to afford 2.23 g (55%) 3-(methylsulfonylmethyl)aniline.

¹H NMR (DMSO-*d*₆): δ 2.77 (3H, s), 3.76 (2H, bs), 4.15 (2H, s), 6.75 (3H, m), 7.18 (1H, t).

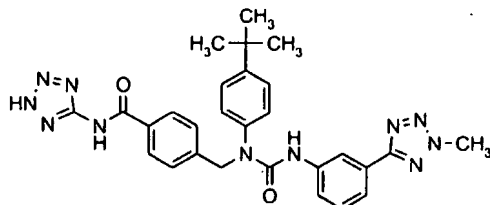
20

The corresponding isocyanate was prepared using the triphosgene method described in example 240.

¹H NMR (DMSO-*d*₆): δ 1.2-1.4 (6H, m), 1.7-1.8 (5H, m), 2.91 (3H, s), 4.40 (2H, s), 5.00 (2H, s), 6.99 (1H, d), 7.2-7.3 (5H, m), 7.46 (4H, m), 8.03 (2H, d), 8.32 (1H, s), 12.4 (1H, s).

25

HPLC-MS (Method B): m/z = 588 (M+1), R_t = 7.48 min.

EXAMPLE 370 (general procedure (M))**4-{1-(4-*tert*-Butylphenyl)-3-[3-(2-methyl-2*H*-tetrazol-5-yl)phenyl]ureidomethyl}-*N*-(2*H*-tetrazol-5-yl)benzamide**

5

3-(2-Methyl-2*H*-tetrazol-5-yl)phenyl isocyanate was prepared as follows:

m-Nitrocyanobenzene (10 g, 67.5 mmol) was dissolved in DMF and ammonium chloride (7.2 g, 135 mmol) and sodium azide (8.8 g, 135 mmol) were added and the resulting mixture was stirred at 125°C for 16 hours. After cooling to room temperature, the mixture was poured into
 10 water (1 L), acidified with 1 N hydrochloric acid and filtered immediately. The mother liquor was left for 1 hour and filtered and the solid was washed with water and dried by suction to afford 9.3 g (72%) 5-(3-nitrophenyl)-2*H*-tetrazole.

¹H NMR (DMSO-*d*₆): δ 7.94 (1H, t), 8.43 (1H, ddd), 8.48 (1H, dt), 8.85 (1H, t).

15

The above 5-(3-nitrophenyl)-2*H*-tetrazole (6.52 g, 34 mmol) was dissolved in DMF (75 mL) and potassium carbonate (14 g) and iodomethane (2.23 mL, 36 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. After evaporation in vacuo, the mixture was partitioned between water (150 mL) and ethyl acetate (100 mL). The aque-
 20 ous phase was extracted with ethyl acetate (100 mL), and the combined organic phases were dried (MgSO₄) and evaporated in vacuo. The residue was washed with a mixture of heptane and diethyl ether to afford 7 g (100%) of a mixture of 1- and 2-methyl-5-(3-nitrophenyl)tetrazole. These isomers were separated using column chromatography.

25 2-Methyl-5-(3-nitrophenyl)-2*H*-tetrazole (2.12 g, 10 mmol) was added ethanol (50 mL) and heated to reflux. At reflux, the mixture was added SnCl₂ dihydrate (11.6 g, 52 mmol) and the mixture was heated at reflux for 2 hours. After cooling, the mixture was poured into ice/water (200 mL) and neutralised (to pH 7) with 1 N sodium hydroxide. The mixture was filtered through celite, and the filter cake was washed with ethyl acetate. For the combined filtrate
 30 and washings the phases were separated and the aqueous phase was extracted with ethyl

acetate (2 x 250 mL). The combined organic phases were dried (MgSO₄) and evaporated in vacuo to afford 3-(2-methyl-2H-tetrazol-5-yl)aniline.

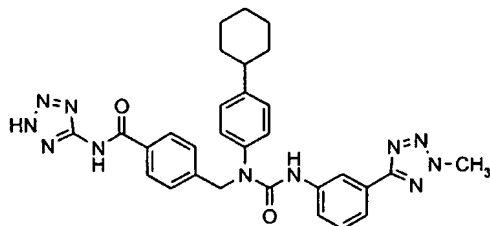
¹H NMR (CDCl₃): δ 3.80 (2H, bs), 4.40 (3H, s), 6.79 (1H, ddd), 7.28 (1H, dd), 7.47 (1H, m),
5 7.51 (1H, dt).

The corresponding isocyanate was prepared using the triphosgene method described in example 240.

10 HPLC-MS (Method B): m/z = 552 (M+1), R_t = 6.58 min.

EXAMPLE 371 (general procedure (M))

4-{1-(4-Cyclohexylphenyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide



15

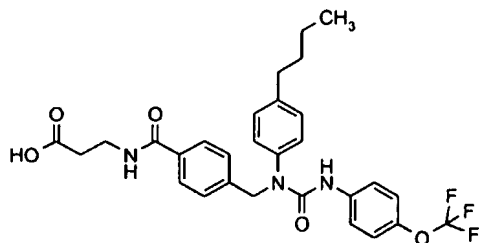
¹H NMR (DMSO-*d*₆): δ 1.2-1.4 (6H, m), 1.6-1.8 (5H, m), 4.40 (3H, s), 5.01 (2H, s), 7.22 (4H, m), 7.40 (1H, t), 7.45 (3H, m), 7.65 (2H, d), 8.01 (2H, d), 8.23 (1H, s), 8.52 (1h, s), 12.0 (1H, bs).

20

HPLC-MS (Method B): m/z = 578 (M+1), R_t = 5.37 min.

EXAMPLE 372

3-{4-[1-(4-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

4-Formylbenzoic acid (15 g, 100 mmol) was dissolved in DMF (250 mL) and 1-hydroxy-benzotriazole (14.9 g, 110 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (21.1 g, 110 mmol) were added and the resulting mixture was stirred at room temperature for 30 minutes. Triethylamine (34.8 mL, 250 mmol) and β -alanine methyl ester hydrochloride (15.4 g, 110 mmol) were added and the resulting mixture was stirred at room temperature for 1 hour. More triethylamine (17.4 mL) and β -alanine methyl ester hydrochloride (7.7 g) were added and the mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic phase was dried (MgSO₄) and concentrated to afford 16.2 g (70%) of 3-(4-formylbenzoylamino)propionic acid methyl ester as an oil.

¹H NMR (CDCl₃): δ 2.70 (2H, t), 3.69 (3H, s), 3.70 (2H, q), 7.68 (1H, bt), 7.9-8.0 (4H, m), 10.1 (1H, s).

The above propionic acid methyl ester (2.0 g, 8.5 mmol) was dissolved in DMF (20 mL) and triethyl orthoformate (10 mL), glacial acetic acid (1 mL), sodium cyanoborohydride (0.81 g, 12.8 mmol) and 4-butylaniline 1.27 g, 8.5 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (100 mL) and washed with saturated aqueous sodium chloride (3 x 100 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (3:1) to afford 1.54 g (49%) of 3-{4-[(4-butylphenylamino)methyl]-benzoylamino}propionic acid methyl ester as an oil.

¹H NMR (CDCl₃): δ 0.92 (3H, t), 1.33 (2H, m), 1.54 (2H, pentet), 2.50 (2H, t), 2.67 (2H, t), 3.72 (5H, m), 4.38 (2H, s), 6.55 (2H, d), 6.83 (1H, bt), 6.98 (2H, d), 7.43 (2H, d), 7.74 (2H, d).

The above propionic acid methyl ester (0.5 g, 1.4 mmol) was dissolved in acetonitrile (10 mL) and added N,N-diisopropylethylamine (232 μL, 1.4 mmol) and 4-(trifluoromethoxy)phenylisocyanate (308 μL, 2.0 mmol) and the resulting mixture was stirred at room temperature for 16 hours. More 4-(trifluoromethoxy)phenylisocyanate (308 μL, 2.0 mmol) was added and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL) and washed with water (3 x 50 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1) containing 1% glacial acetic acid. This afforded 0.53 g (69%) of 3-{4-[1-(4-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester as an oil.

¹H NMR (DMSO-*d*₆): δ 0.98 (3H, t), 1.30 (2H, m), 1.55 (2H, quintet), 2.60 (4H, m), 3.48 (2H, q), 3.61 (3H, s), 4.95 (2H, s), 7.15 (4H, m), 7.22 (2H, d), 7.33 (2H, d), 7.54 (2H, d), 7.75 (2H, d), 8.30 (1H, s), 8.49 (1H, t).

HPLC-MS (Method B): R_t = 8.00 min, m/z = 572 (M+1).

20

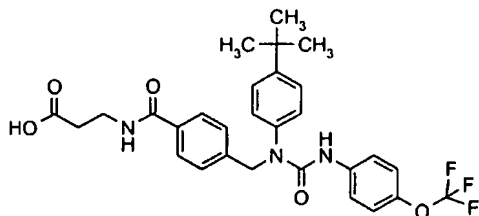
The above propionic acid methyl ester (0.53 g, 0.93 mmol) was dissolved in 1,4-dioxane (50 mL). 4N aqueous sodium hydroxide (6 mL) was added and the resulting mixture was stirred at room temperature for 4 hours. Glacial acetic acid (10 mL) was added and the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL). The aqueous phase was extracted with ethyl acetate (2 x 30 mL), and the combined organic extracts were dried (MgSO₄) and concentrated to afford 0.49 g (95%) of the title compound as an oil.

¹H NMR (CDCl₃): δ 0.94 (3H, t), 1.37 (2H, m), 1.62 (2H, quintet), 2.64 (2H, t), 2.71 (2H, t), 3.73 (5H, m), 4.94 (2H, s), 6.29 (1H, s), 6.87 (1H, t), 7.04 (2H, d), 7.09 (2H, d), 7.21 (2H, d), 7.29 (2H, d), 7.34 (2H, d), 7.68 (2H, d).

30

EXAMPLE 373

3-{4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

The above 3-(4-formylbenzoylamino)propionic acid methyl ester (2.0 g, 8.5 mmol) was dissolved in DMF (20 mL). Triethyl orthoformate (10 mL), glacial acetic acid (1 mL), sodium cyanoborohydride (0.81 g, 12.8 mmol) and 4-*tert*-butylaniline 1.27 g, 8.5 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was added saturated aqueous sodium chloride (100 mL) and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (3 x 100 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1) to afford 0.87 g (30%) of 3-{4-[(4-*tert*-butylphenyl-amino)methyl]benzoylamino}propionic acid methyl ester as an oil.

15

¹H NMR (CDCl₃): δ 1.28 (9H, s), 2.67 (2H, t), 3.73 (5H, m), 4.04 (1H, s), 4.38 (2H, s), 6.57 (2H, d), 6.83 (2H, d), 7.19 (2H, d), 7.44 (2H, d), 7.73 (2H, d).

20 HPLC-MS (Method B): R_t = 6.63 min, m/z = 369 (M+1).

The above propionic acid methyl ester (0.82 g, 2.2 mmol) was dissolved in acetonitrile (15 mL) and added *N,N*-diisopropylethylamine (378 μL, 2.2 mmol) and 4-(trifluoromethoxy)-phenylisocyanate (500 μL, 3.3 mmol). The resulting mixture was stirred at room temperature for 5 hours and at reflux for 16 hours. The cooled reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL) and washed with water (2 x 50 mL), dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from a mixture of ethyl acetate and heptane (1:1) containing 1% glacial acetic acid to afford 0.40 g (32%) of 3-{4-[1-(4-*tert*-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

30

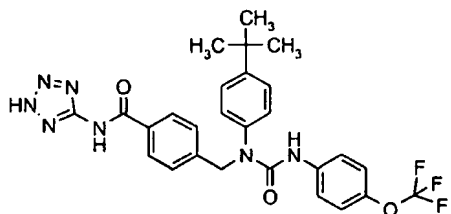
¹H NMR (CDCl₃): δ 1.34 (9H, s), 2.67 (2H, t), 3.72 (5H, m), 4.94 (2H, s), 6.30 (1H, s), 6.80 (1H, t), 7.1 (4H, m), 7.3-7.4 (4H, m), 7.43 (2H, d), 7.70 (2H, d).

The above propionic acid methyl ester (0.25 g, 0.44 mmol) was dissolved in 1,4-dioxane (25 mL). 4N aqueous sodium hydroxide (6 mL) was added and the mixture was stirred at room temperature for 16 hours. 36% aqueous hydrochloric acid (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from a mixture of diethyl ether and heptane to afford 0.10 g (42%) of the title compound as a solid.

¹H NMR (CDCl₃): δ 1.33 (9H, s), 2.70 (2H, t), 3.71 (2H, q), 4.95 (2H, s), 6.32 (1H, s), 6.88 (1H, t), 7.1 (4H, m), 7.28 (2H, d), 7.35 (2H, d), 7.43 (2H,), 7.68 (2H, d).

EXAMPLE 374

4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



4-Formylbenzoic acid methyl ester (10.6 g, 64 mmol) was dissolved in methanol (200 mL). 4-*tert*-Butylaniline (9.61 g, 64 mmol) was added and the resulting suspension was refluxed for 15 minutes. After cooling to room temperature, TFA (5.18 mL, 68 mmol) was added followed by portion wise addition of sodium cyanoborohydride (3.26 g, 52 mmol). The resulting mixture was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was partitioned between ethyl acetate (200 mL) and 1N aqueous sodium hydroxide (150 and 100 mL). The organic phase was dried (MgSO₄) and evaporated in vacuo to afford 19.0 g (99%) of 4-[(4-*tert*-butylphenylamino)methyl]benzoic acid methyl ester as a solid.

¹H NMR (CDCl₃): δ 1.28 (9H, s), 3.92 (3H, s), 4.39 (2H, s), 6.57 (2H, d), 7.20 (2H, d), 7.44 (2H, d), 8.00 (2H, d).

The above benzoic acid methyl ester (0.73 g, 2.44 mmol) was dissolved in acetonitrile (7 mL) and 4-trifluoromethoxyphenylisocyanate (405 μ L, 2.68 mmol) was added. The resulting mixture was stirred at room temperature for 3 hours and then refluxed for 1.5 hour. After cooling and concentration in vacuo, the residue was purified by column chromatography on silica gel, eluting first with a mixture of ethyl acetate and heptane (1:6), then with a mixture of ethyl acetate and heptane (1:3) to afford 1.14 g (94%) of 4-[1-(4-*tert*-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester as an oil.

^1H NMR (CDCl_3): δ 1.35 (9H, s), 3.91 (3H, s), 4.97 (2H, s), 6.30 (1H, s), 7.1 (4H, m), 7.32-7.43 (6H, m), 7.96 (2H, d).

TLC: R_f = 0.11 (SiO_2 ; ethyl acetate/heptane (1:6)).

HPLC-MS (Method B): R_t = 9.05 min, m/z = 501 ($M+1$).

The above ureidomethyl-benzoic acid methyl ester (1.14 g, 2.28 mmol) was dissolved in 1,4-dioxane (25 mL) and added 1N aqueous sodium hydroxide (5 mL). The resulting mixture was stirred at room temperature for 1 hour. Ethanol (15 mL) and 1N aqueous sodium hydroxide (5 mL) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and partitioned between 1N hydrochloric acid (100 mL) and ethyl acetate (2 x 50 mL). The combined organic phases were dried (MgSO_4) and concentrated in vacuo to afford 847 mg (76%) of 4-[1-(4-*tert*-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid as a solid.

^1H NMR (CDCl_3): δ 1.33 (9H, s), 3.91 (3H, s), 4.97 (2H, s), 6.30 (1H, s), 7.1 (4H, m), 7.33 (2H, d), 7.43 (4H, m), 8.03 (2H, d).

HPLC-MS (Method B): R_t = 8.25 min, m/z = 487 ($M+1$).

The above ureidomethyl-benzoic acid (508 mg, 1.04 mmol) was dissolved in dichloromethane (20 mL) and *N,N*-diisopropylethylamine (546 μ L, 3.13 mmol) and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (321 mg, 1.15 mmol) were added. The resulting mixture was stirred at room temperature for 30 minutes. 5-Aminotetrazole hydrate (118 mg, 1.15 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was partitioned between water (200 mL) and ethyl

acetate (2 x 100 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1), containing 1% acetic acid. This afforded 194 mg (34%) of the title compound as a solid.

5

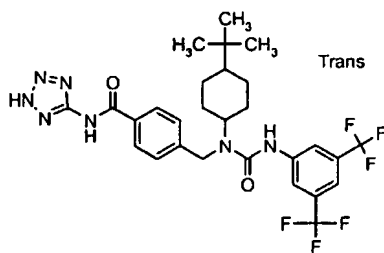
^1H NMR (CDCl_3): δ 1.33 (9H, s), 3.91 (3H, s), 5.01 (2H, s), 6.35 (1H, s), 7.10 (2H, d), 7.14 (2H, d), 7.36 (2H, d), 7.45 (2H, d), 7.58 (2H, d), 8.22 (2H, d), 12.3 (1H, s).

HPLC-MS (Method B): R_t = 7.95 min, m/z = 554 ($M+1$).

10

EXAMPLE 375

4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

This compound was prepared similarly as described in example 374 starting from *trans*-4-[(4-*tert*-butylcyclohexylamino)methylbenzoic acid methyl ester (prepared as described in general procedure (K), step 1) followed by reaction with 3,5-bis(trifluoromethyl)phenyl isocyanate, hydrolysis and coupling with 5-aminotetrazole.

20

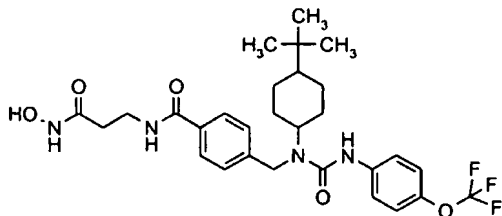
HPLC-MS (method B): m/z : 612. R_t = 8.38 min.

^1H NMR (DMSO_d): δ 0.83 (9H, s), 0.96 (1H, m), 1.14 (2H, m), 1.44 (2H, m), 1.73 (4H, m), 4.09 (1H, m), 4.68 (2H, s), 7.45 (2H, d), 7.63 (1H, s), 8.07 (2H, d), 8.29 (2H, s), 9.08 (1H, s), 12.49 (1H, s).

25

EXAMPLE 376

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2-hydroxycarbamoyl)benzamide



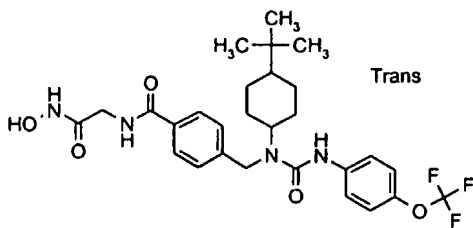
5

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid (prepared as described in example 92; 0.2 g, 0.36 mmol) was dissolved in DMF (5 mL) and 1-hydroxybenzotriazole (53 mg, 0.39 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (75 mg, 0.39 mmol) were added and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was cooled to 0°C and *N,N*-diisopropylethylamine (85 µL, 0.50 mmol) and *O*-(trimethylsilyl)hydroxylamine (60 µL, 0.50 mmol) were added and the mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (50 mL) and was washed with a saturated aqueous solution of sodium chloride (50 mL). The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and glacial acetic acid (9:1). This afforded 95 mg (46%) of the title compound as a solid.

20 HPLC-MS (Method B): *R*_t = 7.32 min, *m/z* = 579 (*M* + 1).

EXAMPLE 377

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-hydroxycarbamoylmethyl-benzamide



25

This compound was prepared from 3-{4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}acetic acid (example 95), by coupling this compound with O-trimethylsilylhydroxylamine using standard peptide coupling conditions as described in the art.

5

^1H NMR ($\text{DMSO}-d_6$): δ 10.60 (1H, s), 8.78 (1H, s), 8.65 (1H, t), 8.52 (1H, s), 7.80 (2H, d), 7.55 (2H, d), 7.34 (2H, d), 7.23 (2H, d), 4.60 (2H, broad), 4.05 (1H, m), 3.75 (2H, d), 1.80-0.85 (10H, m), 0.80 (9H, s).

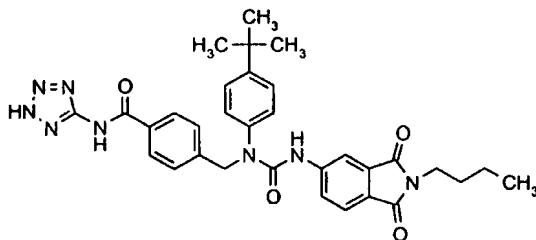
10 Micro analysis. Calculated for $\text{C}_{28}\text{H}_{35}\text{F}_3\text{N}_4\text{O}_5$, $0.75\text{H}_2\text{O}$:

C, 58.17%; H, 6.36%; N, 9.69%. Found:

C, 58.29%; H, 6.28%; N, 9.97%.

EXAMPLE 378

15 4-[3-(2-Butyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



To a solution of 4-nitrophthalimide (7.20 g, 37.5 mmol) and n-bromobutane (25.5 g; 186 mmol) in DMF (50 mL) was added potassium carbonate (10.0 g; 72.5 mmol) and the resulting mixture was heated to 100°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was separated, washed once with brine and dried with anhydrous Na_2SO_4 . The solvent was removed in vacuo by rotary evaporation to leave *N*-butyl-4-nitrophthalimide as an oil, which crystallised upon standing. Yield: 9.37 g (100%).

25

^1H NMR ($\text{DMSO}-d_6$): δ 0.91 (t, 3H); 1.31 (m, 2H); 1.60 (m, 2H); 3.62 (t, 2H); 8.11 (d, 1H); 8.47 (d, 1H); 8.61 (dd, 1H).

30 A solution of *N*-butyl-4-nitrophthalimide (1.45 g, 5.8 mmol) in methanol (30 mL) was added drop wise to a well stirred solution of sodium dithionite (6.50 g, 37.1 mmol) and sodium car-

bonate (3.22 g, 30.5 mmol) in water (40 mL), while the temperature was maintained at 70°C. After addition, heating at 70°C was continued for a further 30 minutes, then the reaction mixture was allowed to cool to room temperature. The reaction volume was reduced to one third by rotary evaporation, and the residual water solution was extracted with diethyl ether (2 x 50 mL). The combined organic phases were dried with anhydrous Na₂SO₄, and then taken to dryness. The residual oil was recrystallised from ethanol/water to give 750 mg (59%) of *N*-butyl-4-aminophthalimide.

¹H NMR (DMSO-*d*₆): δ 0.89 (t, 3H); 1.26 (m, 2H); 1.53 (m, 2H); 3.48 (t, 2H); 6.44 (bs, 2H); 6.78 (dd, 1H); 6.92 (d, 1H); 7.46 (d, 1H).

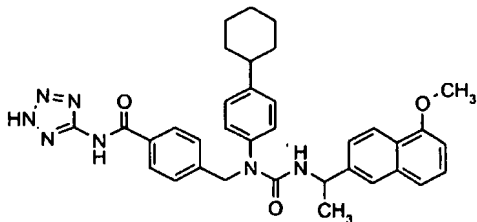
N-Butyl-4-aminophthalimide (100 mg, 0.46 mmol) was suspended in toluene (2 mL), and bis(trichloromethyl)carbonate (50 mg, 0.17 mmol) was added. The mixture was heated to reflux for 1 hour, then cooled and taken to dryness by rotary evaporation. The solid residue was re-dissolved in DMF (2 mL). 4-[(4-*tert*-Butylphenylamino)methyl]-*N*-2*H*-tetrazol-5-yl)benzamide (161 mg, 0.46 mmol) was added and the mixture heated to 100°C for 2 hours. After cooling to room temperature, water (3 mL) was added and the precipitated gum collected by filtration. Recrystallisation from acetonitrile afforded the title compound as a white powder. Yield: 20 mg (30%).

¹H NMR (DMSO-*d*₆): δ 0.88 (t, 3H); 1.25 (m, 2H); 1.28 (s, 9H); 1.55 (m, 2H); 3.54 (t, 2H); 5.03 (s, 2H); 7.25 (d, 2H); 7.42 (d, 2H); 7.48 (d, 2H); 7.72 (d, 1H); 7.80 (d, 1H); 8.02 (s, 1H); 8.04 (d, 2H); 8.95 (s, 1H); 12.26 (bs, 1H).

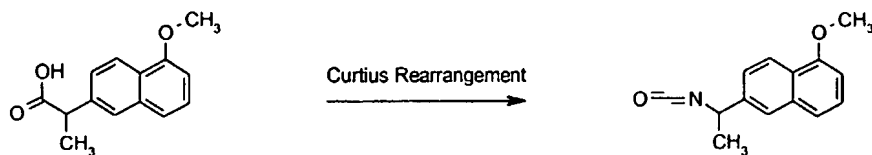
HPLC-MS (method B): 595.4 (M+1). R_t = 7.68 min.

EXAMPLE 379

4-{1-(4-Cyclohexylphenyl)-3-[1-(5-methoxynaphthalen-2-yl)ethyl]ureidomethyl}-*N*-(2*H*-tetrazol-5-yl)benzamide



The isocyanate was prepared *in situ* via a Curtius rearrangement of the corresponding carboxylic acid:



5

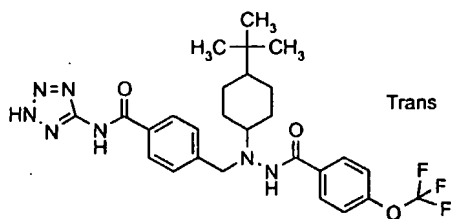
2-(5-Methoxynaphthalen-2-yl)propionic acid (0.26 g, 1.12 mmol) was dissolved in toluene (10 mL). Triethylamine (0.52 mL) was added followed by diphenylphosphoryl azide (0.40 mL, 1.86 mmol). The mixture was stirred for 2 hours at 25°C and 4-[(4-cyclohexylphenylamino)-methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (0.14 g, 0.37 mmol) was added. Stirring was continued at 25°C for 16 hours then at 100°C overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel using a mixture of heptane and ethylacetate (1:1) as eluent to afford the title compound.

¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.05 (d, 2H); 7.72 (d, 2H); 7.62 (s, 1H); 7.45-7.35 (m, 3H); 7.28 (s, 1H); 7.25-7.10 (m, 5H); 5.05 (m, 1H); 4.93 (d, 2H); 3.86 (s, 3H); 1.75-1.65 (m, 4H); 1.50-1.15 (m, 9H)

HPLC-MS (Method B): *m/z* = 604 (*M*+1). *R*_t = 8.08 min.

20 EXAMPLE 380

4-[*N*-(*trans*-4-*tert*-Butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



25 *Trans*-4-trifluoromethoxybenzoic acid *N'*-(4-*tert*-butylcyclohexyl)hydrazide (350 mg, 1.0 mmol) and methyl 4-(bromomethyl)benzoate (220 mg, 1.0 mmol) were dissolved in DMF (5.0 mL). Sodium hydrogen carbonate (300 mg) was added, and the mixture was stirred for 16 hours under a nitrogen atmosphere at ambient temperature. Water (30 mL) was added and

the mixture was extracted with diethyl ether (2 x 25 mL). The combined organic phases were dried with Na₂SO₄ and evaporated in vacuo to afford methyl 4-[*N*-(4-*tert*-butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethylbenzoate as white crystals. Yield: 430 mg (85%).

- 5 ¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H); 0.95 (m, 3H); 1.23 (m, 2H); 1.78 (m, 2H); 2.06 (m, 2H); 3.82 (s, 3H); 4.14 (s, 2H); 7.38 (d, 2H); 7.54 (d, 2H); 7.71 (d, 2H); 7.85 (d, 2H); 9.24 (s, 1H).

- Methyl 4-[*N*-(4-*tert*-butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethylbenzoate (400 mg, 0.78 mmol) was dissolved in methanol (40 mL) by gentle heating. After cooling to
10 room temperature, aqueous sodium hydroxide (4 mL; 4N) was added. The mixture was heated to reflux for 2 hours, then allowed to cool to ambient temperature. Acetic acid (3.0 mL) was added before the solvent was removed in vacuo. Water (30 mL) was added to the residue, and insoluble material was collected by filtration. Recrystallisation from acetonitrile afforded 4-[*N*-(4-*tert*-butylcyclohexyl)-*N'*-(4-trifluoromethoxy-benzoyl)hydrazinomethylbenzoic
15 acid. Yield: 320 mg (83%).

- ¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H); 0.96 (m, 3H); 1.24 (m, 2H); 1.78 (m, 2H); 2.05 (m, 2H); 2.85 (t, 1H); 4.13 (s, 2H); 7.38 (d, 2H); 7.50 (d, 2H); 7.72 (d, 2H); 7.82 (d, 2H); 9.26 (s, 1H).
- 20 HPLC-MS (method B): 493.2 (M+1). R_t = 7.92 min.

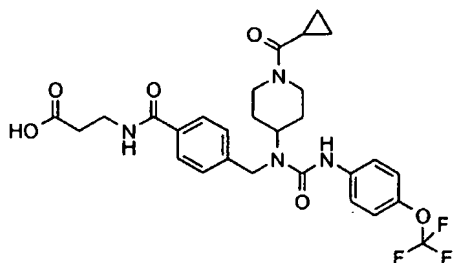
- 4-[*N*-(4-*tert*-Butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethylbenzoic acid (264 mg; 0.54 mmol), *N*-hydroxybenzotriazole monohydrate (82 mg, 0.54 mmol) and *N*-ethyl-*N'*-3-dimethylaminopropylcarbodiimide hydrochloride (105 mg, 0.54 mmol) were dissolved in DMF
25 (4.0 mL). The mixture was stirred at room temperature for 30 minutes, and then 5-amino-tetrazole monohydrate (100 mg; 0.96 mmol) was added. The reaction mixture was then left stirring at ambient temperature for 48 hours. The mixture was poured in water (40 mL), and the precipitated material collected by filtration. After several washes with water, the material was dried in vacuo to afford the title compound as a white powder. Yield: 257.2 mg; (86%).

- 30 ¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H); 0.98 (m, 3H); 1.25 (m, 2H); 1.80 (m, 2H); 2.07 (m, 2H); 4.16 (s, 2H); 7.38 (d, 2H); 7.59 (d, 2H); 7.73 (d, 2H); 8.02 (d, 2H); 9.26 (s, 1H); 12.27 (bs, 1H).

- 35 HPLC-MS (method B): 560.4 (M+1). R_t = 7.77 min.

EXAMPLE 381

3-{4-[1-(1-Cyclopropanecarbonylpiperidin-4-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid



5

4-[1-[4-(2-Methoxycarbonylethylcarbamoyl)benzyl]-3-(4-trifluoromethoxyphenyl)ureido]-piperidine-1-carboxylic acid *tert*-butyl ester

- 4-[1-[4-(2-Methoxycarbonylethylcarbamoyl)benzyl]-3-(4-trifluoromethoxyphenyl)ureido]-piperidine-1-carboxylic acid *tert*-butyl ester was prepared in analogy with previously described methods (reductive amination using 4-aminopiperidine-1-carboxylic acid *tert*-butyl ester).

3-{4-[1-Piperidin-4-yl-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester hydro chloride

The Boc-protecting group was removed by adding 20 mL HCl in ethyl acetate (2M) to a suspension of 4-[1-[4-(2-methoxycarbonylethylcarbamoyl)benzyl]-3-(4-trifluoromethoxy-phenyl)-ureido]piperidine-1-carboxylic acid *tert*-butyl ester (2.60 g) in 25 mL ethyl acetate. Stirring overnight at 25°C followed by evaporation of the solvent afforded the desired compound.

20

3-{4-[1-(1-Cyclopropanecarbonylpiperidin-4-yl)-3-(4-trifluoromethoxy-phenyl)ureidomethyl]-benzoylamino}propionic acid methyl ester

To a solution of 3-{4-[1-piperidin-4-yl-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester hydrochloride (0.20 g) in DMF (5 mL) was added diisopropylethylamine (0.30 mL) and cyclopropylcarboxylic acid chloride (0.16 mL). The mixture was stirred at 25°C overnight. Water (100 mL) and ethyl acetate (100 mL) were added, the phases separated and the organic phase was washed with a solution of NH₄Cl (sat., 2 x 50 mL) and water (50 mL). Upon drying with MgSO₄ the solvent was evaporated and the residue purified by column chromatography.

30

3-{4-[1-(1-Cyclopropanecarbonylpiperidin-4-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

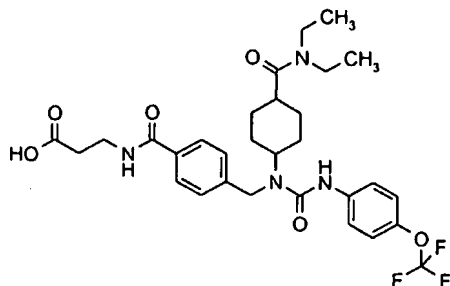
The above 3-{4-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoylamino}propionic acid methyl ester (0.17 g, 0.28 mmol) was dissolved in 10 mL ethanol and hydrolysed by adding lithium hydroxide (14 mg, 0.56 mmol) dissolved in water (1 mL). The mixture was stirred at 50°C for 2 hours. The solvent was evaporated and water (25 mL) was added to the mixture followed by HCl (1N) adjusting pH to 3-4 allowing the title compound to be isolated as a precipitate.

¹H NMR (300 MHz, DMSO-*d*₆): δ 12.22 (s br, 1H); 8.60 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.32 (d, 2H); 7.22 (d, 2H); 4.62 (s, 2H); 4.50-4.30 (m, 3H); 3.45 (q, 2H); 3.05 (t br, 1H); 2.50 (t, 2H); 1.95 (m, 1H); 1.70-1.40 (m, 4H); 0.70 (m, 4H).

HPLC-MS (method B): *m/z* = 577, *R*_t = 5.40 min.

EXAMPLE 382

3-{4-[1-(4-Diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



4-[(4-Carboxycyclohexylamino)methyl]benzoic acid methyl ester

Methyl 4-formylbenzoate (5 g, 30 mmol) was dissolved in DMF (60 mL) and 4-aminocyclohexylcarboxylic acid (4.36 g, 30 mmol) and NaBH₄ (1.1 g, 30 mmol) were added. The mixture was stirred at 70°C overnight. Trimethylorthoformate (10 mL) was added and the mixture was stirred at 100°C overnight. Toluene was added and the mixture was heated to 135°C and stirred overnight. The solvent was evaporated leaving a DMF solution to which HCl (1N, 30 mL) was added causing precipitation. The desired product was collected by filtration.

4-[1-(4-Carboxycyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester

The above 4-[(4-carboxycyclohexylamino)methyl]benzoic acid methyl ester (1g, 3.4 mmol) was dissolved in acetonitrile (25 mL) and 4-trifluoromethoxyphenylisocyanate (0.73 g, 3.4 mmol) was added. Stirring overnight at 50°C followed by cooling to 25°C formed a precipitate, which was removed by filtration. The filtrate was concentrated *in vacuo* and the product purified by chromatography using silica as stationary phase and a mixture of ethyl acetate, methanol and acetic acid as eluent (15:1:0.1).

4-[1-(4-Diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester

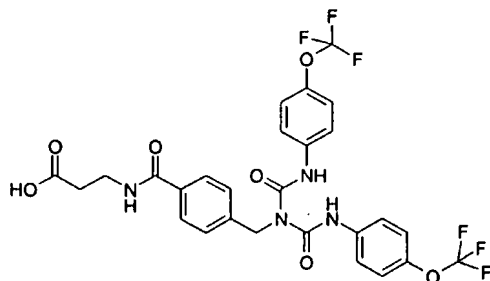
To the above 4-[1-(4-carboxycyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester (0.30 g, 0.6 mmol) dissolved in DMF (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC, 0.12 g, 0.6 mmol) and 1-hydroxybenzotriazole (HOBt, 0.098g, 0.65 mmol). After stirring the mixture 30 min at 25°C, diethylamine (76 µL) was added. The mixture was allowed to react overnight at 25°C. Water (100 mL) and ethyl acetate (100 mL) were added, the phases separated and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried with MgSO₄ and evaporated to give the desired product.

3-{4-[1-(4-Diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

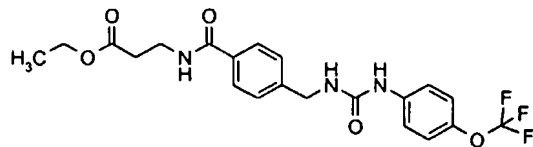
The above 4-[1-(4-diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester was converted into the title compound by methods already described.

¹H NMR (300 MHz, DMSO-*d*₆): δ 12.22 (s br, 1H); 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.55 (s, 2H); 4.10 (t br, 1H); 3.45 (q, 2H); 3.20 (m, 2H); 2.70 (s br, 1H); 2.10-1.40 (m, 8H); 1.10 (t, 3H); 0.95 (t, 3H).

HPLC-MS (method B): m/z = 607, R_t = 6.50 min.

EXAMPLE 383**3-{4-[1,5-Bis(4-trifluoromethoxyphenyl)-3-biuretmethyl]benzoylamino}propionic acid**

- 5 Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride was prepared from β -alanine ethyl ester hydrochloride and 4-(*tert*-butoxycarbonylaminomethyl)benzoic acid by methods known to those skilled in the art.

3-(4-[3-(4-Trifluoromethoxyphenyl)ureidomethyl]benzoylamino)propionic acid ethyl ester

10

- Ethyl 3-(4-Aminomethylbenzoylamino)propanoate hydrochloride (0.25 g, 0.87 mmol) in acetonitrile (5 mL) and diisopropylethylamine (0.15 mL) was allowed to react with 4-trifluoromethoxyphenylisocyanate (0.37 g, 1.74 mmol) at 50°C overnight. Upon cooling to 25°C the product precipitated and was collected by filtration.

15

3-(4-[1,5-Bis(4-trifluoromethoxyphenyl)-3-biuretmethyl]benzoylamino)propionic acid ethyl ester

- To a solution of the above 3-(4-[3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino)propionic acid ethyl ester (0.32 g, 0.71 mmol) in DMF (5 mL) was added sodium hydride (17 mg, 0.71 mmol). The mixture was stirred at 25°C for 1hr. Then 4-trifluoromethoxyphenylisocyanate (0.22 g, 1.06 mmol) was added and the mixture was stirred 5 hours at 25°C. The product was isolated by filtration.

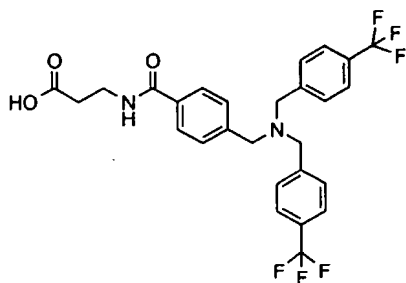
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3-{4-[1,5-Bis(4-trifluoromethoxyphenyl)-3-biuret-methyl]-benzoylamino}-propionic acid

The above 3-{4-[1,5-bis(4-trifluoromethoxyphenyl)-3-biuret-methyl]benzoylamino}propionic acid ethyl ester was hydrolysed into the title compound by methods already described.

- 5 ^1H NMR (300 MHz, DMSO- d_6): δ 12.22 (s br, 1H); 10.20 (s, 2H); 7.75 (d, 2H); 7.55 (d, 4H); 7.42 (d, 1H); 7.32 (d, 4H); 5.10 (s, 2H); 3.45 (q, 2H).

HPLC-MS (method B): m/z = 629, R_t = 7.61 min.

10 EXAMPLE 3843-(4-{[Bis(4-trifluoromethylbenzyl)amino]methyl}benzoylamino)propionic acidResin bound Fmoc β -alanine

- 15 150 μmol Fmoc β -alanine was dissolved in a mixture of 250 μL dichloromethane, 250 μL DMF and 100 μL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine (17:2:1) and 2 x 1 mL DMF.

Resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}-propionic acid

To the above resin bound Fmoc β -alanine was added 500 μ L of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF contain-
5 ing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200 μ mol 4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoic acid (74.2 mg) dissolved in a mixture of 430 μ L DMF and 70 μ L diethylisopropylamine was added followed by 200 μ mol bromo-tris-pyrro-
lidinophosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500 μ L DMF. The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with 3
10 x 1 mL DMF.

Resin bound 3-(4-{[bis(4-trifluoromethylbenzyl)amino]methyl}benzoylamino)propionic acid

The Fmoc protecting group was removed from the above resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}propionic acid using 500 μ L of a 20% solution
15 of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL), 2 x 1 mL 1,2-di-
chloroethane and 20 μ L acetic acid dissolved in 1 mL 1,2-dichloroethane.

The resulting resin bound 3-(4-aminomethylbenzoylamino)propionic acid was treated with 98
20 mg 4-trifluoromethylbenzaldehyde (700 μ mol) dissolved in 500 μ L 1,2-dichloroethane, 50 μ L acetic acid and a slurry of 148 mg NaBH(OAc)₃ (700 μ mol) in 1 mL 1,2-dichloroethane.
Overnight shaking at 25°C followed by filtration and washing with 2 x 1 mL dichloromethane,
2 x 1 mL CH₃OH:DMF (1:1) and 3 x 1 mL DMF afforded resin bound 3-(4-{[bis(4-trifluoro-
methylbenzyl)amino]methyl}-benzoylamino)propionic acid.

25

3-(4-{[Bis(4-trifluoromethylbenzyl)amino]methyl}benzoylamino)propionic acid

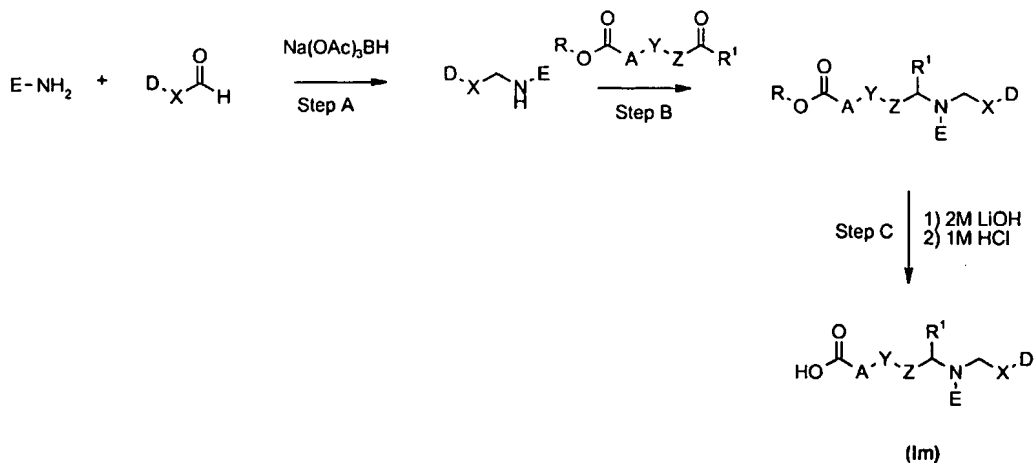
The above resin bound 3-(4-{[bis(4-trifluoromethylbenzyl)amino]methyl}benzoylamino)-
propionic acid was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The
product was filtered off and the resin was washed with 1 mL dichloromethane. The combined
30 extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L
CH₃CN and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 μ col-
umn. The starting eluent composition was 5% CH₃CN in H₂O changing over 30 minutes to
90% CH₃CN in H₂O which was then kept constant for 5 minutes before going back to the
starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one
35 fraction per min. The process was monitored using a UV detector operating at 214 nm. The

fractions containing the desired products were combined and evaporated in vacuo to afford the title compound.

¹H NMR (300 MHz, DMSO-*d*₆): δ 8.48 (t, 1H); 7.82 (d, 2H); 7.72 (d, 2H); 7.62 (d, 2H); 7.45 (d,
5 2H); 3.85 (br, 6H).

HPLC-MS (method B): m/z = 539, 5.90 min.

General procedure (N) for the solution phase synthesis of compounds of the general formula (Im):



5 wherein

A, Y, Z, E, X, D and R¹ are as defined for formula (I) and

R is C₁₋₈-alkyl.

10

Step A:

The appropriate carbonyl in dichloromethane was reacted with the desired amines (1.1 eq) in dichloromethane. To this solution was added sodium triacetoxyborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was left to proceed for 15 hours.

15 The reactions were diluted with ethyl acetate and washed with saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over MgSO₄. Evaporation of the solvent afforded the crude desired amine.

Step B:

20 To the amine from step A in dichloromethane was added R-OC(O)-A-Y-Z-C(O)-R¹, eg ethyl 3-[(4-formylbenzoyl)amino]]propionate, (0.9 eq) in dichloromethane. R-O(CO)-A-Y-Z-C(O)-R¹ may be prepared in a similar way as described in the general procedure (J) under the general preparation of formylarylcarboxamides. To this solution was added sodium triacetoxyborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was
25 left to proceed for 15 hours. The reactions were diluted with ethyl acetate and washed with

saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over MgSO_4 . Evaporation of the solvent afforded the crude desired amine.

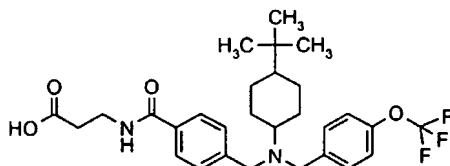
Step C:

- 5 The residue obtained in step B was dissolved in DMF and aqueous 2M lithium hydroxide (10 eq) was added. The reactions were shaken overnight and filtered.

The following examples were prepared according to the general procedure (N).

10 EXAMPLE 385 (general procedure (N))

3-(4-(((4-*tert*-Butylcyclohexyl)-(4-trifluoromethoxybenzyl)amino)methyl)benzoylamino)-propionic acid



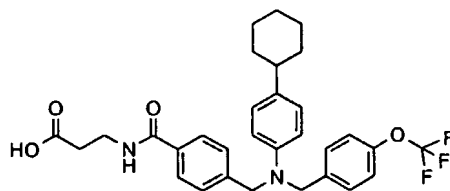
- 15 ^1H NMR ($\text{DMSO}-d_6$): δ 0.79 (s, 9H), 0.86 – 1.05 (m, 3H), 1.60 (qt, 2H), 1.82 (d, 2H), 2.27 (d, 2H), 2.50 (t, 2H), 3.02 (t, 1H), 3.45 (qt, 2H), 4.18 (m, 2H), 4.50 (m, 2H), 7.36 (d, 2H), 7.62 (d, 2H), 7.34 (d, 2H), 7.81 (d, 2H), 8.63 (t, 1H), 10.80 (brd s, 1H), 12.00 (brd s, 1H).

MS (APCI, pos): 535.2, 536.2, 537.2.

20

EXAMPLE 386 (general procedure (N))

3-(4-(((4-Cyclohexylphenyl)-(4-trifluoromethoxybenzyl)amino)methyl)benzoylamino)propionic acid



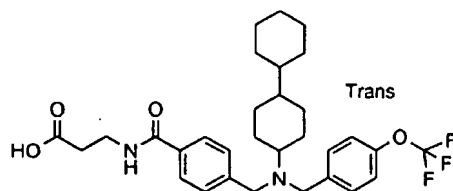
25

^1H NMR ($\text{MeOH}-d_4$): δ 0.95 – 1.15 (m, 5H), 1.40 – 1.52 (m, 5H), 2.12 (m, 1H), 2.39 (t, 2H), 3.39 (qt, 2H), 4.47 – 4.49 (m, 4H), 6.51 (d, 2H), 6.77 (d, 2H), 6.91 (d, 2H), 7.06 (m, 4H), 7.50 (d, 2H).

MS (APCI, pos): 552.2

EXAMPLE 387 (general procedure (N))

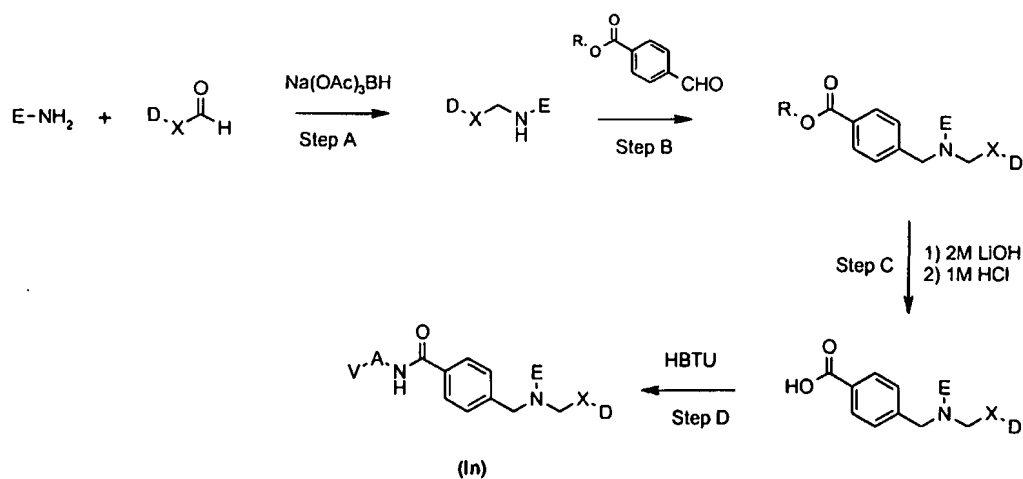
- 5 3-(4-(((trans-4-Cyclohexylcyclohexyl)-(4-trifluoromethoxybenzyl)amino)methyl)benzoyl-amino)propionic acid



- ¹H NMR (DMSO-*d*₆): δ 0.80 – 1.06 (m, 10H), 1.20 (qt, 2H), 1.51 – 1.90 (m, 9H), 2.14 (t, 2H),
10 2.20 (m, 1H), 3.33 (t, 2H), 3.57 (brd m, 4H), 7.22 (d, 2H), 7.37 (d, 2H), 7.42 (d, 2H), 7.68 (d, 2H).

MS (APCI, pos): 561.2, 562.2, 489.2.

- 15 General procedure (O) for the solution phase synthesis of compounds of the general formula (In):



- 20 wherein

E, X, D, A, and V are as defined in formula (I), and

R is C₁₋₆-alkyl.

Step A:

- 5 The appropriate carbonyl compound, D-X-CHO, in dichloromethane was reacted with the desired amines (1.1 eq) in dichloromethane. To this solution was added sodium triacetoxyborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was left to proceed for 15 hours. The reactions were diluted with ethyl acetate and washed with saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over MgSO₄. Evaporation of the solvent afforded the crude desired amine.
- 10

Step B:

- To the amine from step A in dichloromethane was added C₁₋₆-alkyl 4-formylbenzoate (0.9 eq) in dichloromethane. To this solution was added sodium triacetoxyborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was left to proceed for 15 hours. The reactions were diluted with ethyl acetate and washed with saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over MgSO₄. Evaporation of the solvent afforded the crude desired amine.
- 15

20 Step C:

The residue obtained in step B was dissolved in DMF and aqueous 2M lithium hydroxide (10 eq) were added. The reactions were shaken overnight, diluted with ethyl acetate and washed with water (3 x), brine, dried over MgSO₄, filtered, and concentrated.

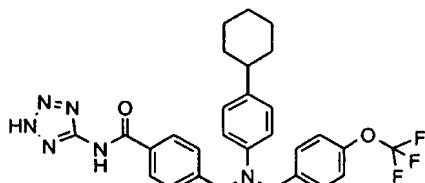
25 Step D:

- To a solution of the acid from step C in a suitable solvent such as dichloromethane, DMF, or THF was added diisopropylethylamine (5 eq) and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (1.1 eq). The reaction was allowed to stir for 30 minutes before 5-aminotetrazole hydrochloride (3 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1 N HCl. The organic layer was separated and washed with H₂O (2 x), aqueous NaHCO₃ (3 x), brine (2 x), dried over MgSO₄, and concentrated to give the desired product.
- 30

- 35 The following examples were prepared according to the general procedure (O).

EXAMPLE 388 (general procedure (O))

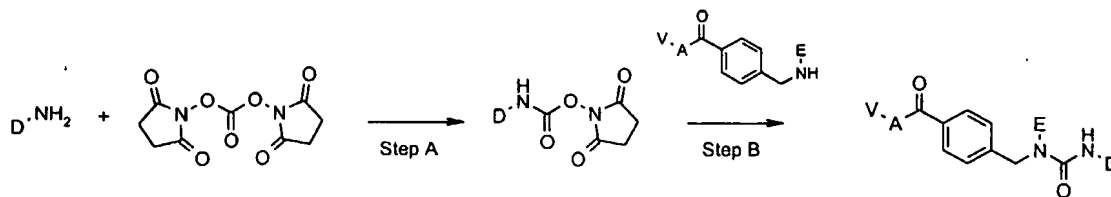
4-[[[(4-Cyclohexylphenyl)-(4-trifluoromethoxybenzyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide



^1H NMR ($\text{DMSO}-d_6$): δ 1.28 (m, 5H), 1.70 (m, 5H), 2.30 (m, 1H), 4.74 (s, 2H), 4.77 (s, 2H), 6.57 (d, 2H), 6.95 (d, 2H), 7.32 – 7.44 (m, 6H), 8.07 (d, 2H), 12.40 (brd s, 1H), 15.90 (brd s, 1H).

MS (APCI, Neg): 549.2, 550.2, 551.2.

General procedure (P) for solution phase synthesis of compounds of the general formula (Io):



wherein

E and D are as defined in formula (I),

A is $-\text{CH}_2-\text{CH}_2-\text{NH}-$ or $-\text{NH}-$ and

V is tetrazol-5-yl or $\text{C}(\text{O})\text{OR}^2$, wherein R^2 is hydrogen or C_{1-6} -alkyl.

Step A:

The appropriate primary amine (0.011 mmol) in acetonitrile was dispensed into reactor tubes containing *N,N'*-disuccinimidyl carbonate (0.011 mmol) in acetonitrile. The solutions were

stirred at room temperature for 4 hours to give the corresponding carbamates in quantitative yields.

Step B:

- 5 To the resulting carbamates from step A was added the corresponding amine (0.011 mmol) in acetonitrile. The reactions were stirred at 80°C overnight. Evaporation of the solvent under reduced pressure gave the desired urea.

- 10 In case V is C(O)OC₁₋₆-alkyl, a third synthesis step C may be added where C(O)OC₁₋₆-alkyl is hydrolysed to C(O)OH.

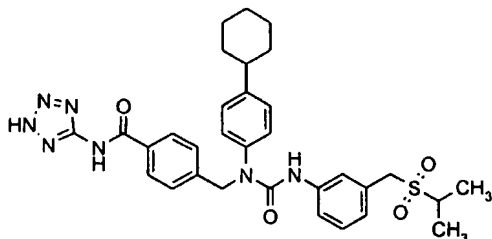
Step C:

- The residue obtained in step B was dissolved in DMF and aqueous 2 M lithium hydroxide (10 eq.) were added into each reaction vessel. The samples were shaken overnight and filtered.
- 15 Aqueous 1 N HCl was then added to give the desired carboxylic acids.

The following examples were prepared according to the general procedure (P).

EXAMPLE 389 (General procedure (P))

- 20 4-{1-(4-Cyclohexylphenyl)-3-[3-(propane-2-sulfonylmethyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide



- To a solution of 3-nitrobenzyl bromide (3 g, 13.9 mmol) and 2-propanethiol (1.16 g, 15.3 mmol) in THF (100 mL) was added CsCO₃ (6.5 g, 20 mmol). The mixture was refluxed for 16 hours, and filtered. To the filtrate was added excess 3-chloroperoxybenzoic acid. The mixture was stirred at room temperature for 16 hours, concentrated to one-third volume, diluted with water (100 mL), and extracted with ether. The organic extracts were washed with 10% sodium carbonate, dried (Na₂SO₄), and concentrated to provide a mixture containing desired product and starting material. After column chromatography on silicagel, eluting with a mix-
- 25
- 30

ture of hexane and ethyl acetate (2:1) pure isopropyl 3-nitrobenzyl sulfone (2.7 g, 80%) was isolated.

¹H NMR (CDCl₃): δ 1.42 (d, 6H), 3.09 (m, 1H), 4.29 (s, 2H), 7.59 (t, 1H), 7.79 (d, 1H), 8.2-8.3 (s overlap with d, 2H).

To a solution of the above isopropyl 3-nitrobenzyl sulfone (1.4 g, 5.8 mmol) in ethanol (50 mL) was added 100 mg Pd/C(10%). The mixture was stirred under a hydrogen atmosphere at room temperature for 30 min. The catalyst was filtered off, and the filtrate was concentrated to give the isopropyl 3-aminobenzyisulfone.

¹H NMR (CDCl₃): δ 1.32 (d, 6H), 3.02 (m, 1H), 4.15 (s, 2H), 6.65 - 6.82 (m, 3H), 7.14 (t, 1H).

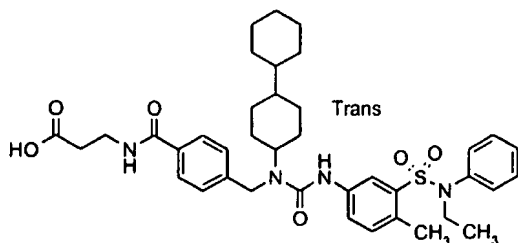
This title compound was prepared from isopropyl 3-aminobenzyisulfone and 4-[(4-cyclohexyl-anilino)methyl]-N-(2H-tetrazol-5-yl)benzamide following the general procedure for formation of ureas with di-(N-succinimidyl)carbonate.

¹H NMR (DMSO-*d*₆) δ: 1.27 (d, 6H), 1.28-1.45 (m, 6H), 1.62-1.88 (m, 5H), 3.20 (m, 1H), 4.36 (s, 2H), 4.99 (s, 2H), 7.00 (d, 1H), 7.15-7.30 (m, 3H), 7.47 - 7.55 (m, 4H), 7.98 (d, 2H), 8.28 (s, 1H), 11.3 (br, 1H).

LC-MS (APCI, pos.): 616 (M+1).

EXAMPLE 390 (general procedure (P))

25 3-(4-{1-(*trans*-4-Cyclohexylcyclohexyl)-3-[3-(*N*-ethyl-*N*-phenylsulfamoyl)-4-methylphenyl]-ureidomethyl}benzoylamino)propionic acid

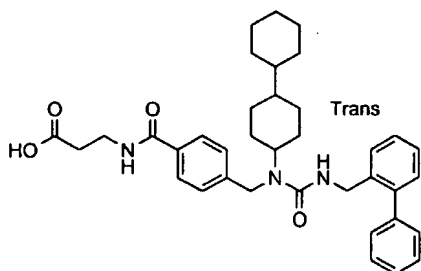


^1H NMR ($\text{DMSO}-d_6$): δ 0.90 - 1.30 (m, 13H), 1.39 (q, 2H), 1.65 (m, 8H), 2.14 (s, 3 H), 2.48 (m, 2H), 3.59 (m, 2H), 3.32 (q, 2H), 4.03 (m, 1H), 4.59 (s, 2H), 7.18 (m, 3H), 7.33 (m, 5H), 7.67 (d, 1H), 7.73 (d, 2H), 7.96 (s, 1H), 8.43 (m, 1H), 8.58 (s, 1 H).

5 MS (APCI, pos.): 703.3 (M+1).

EXAMPLE 391 (general procedure (P))

3-(4-{1-(*trans*-4-Cyclohexylcyclohexyl)-3-biphenyl-2-ylmethyl}ureidomethyl)benzoyl-amino)propionic acid



10

^1H NMR ($\text{DMSO}-d_6$): δ 0.62- 1.25 (m, 10H), 1.39 (q, 2H), 1.60 (m, 8H), 2.46 (m, 2 H), 3.43 (q, 2H), 3.85 (m, 1H), 3.97 (d, 2H), 4.44 (s, 2H), 6.50 (s, 1 H), 6.94 (d, 1H), 7.02 -7.23 (m, 10H), 7.52 (d, 2H), 7.75 (d, 2H), 8.23 (t, 1H).

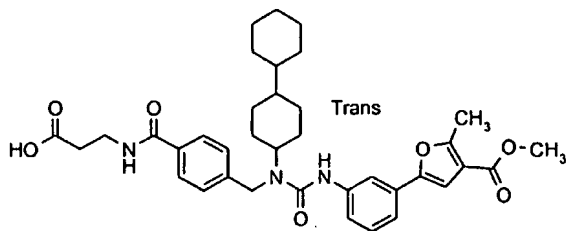
15

MS (APCI, pos.): 596.4 (M+1).

EXAMPLE 392 (general procedure (P))

5-(3-(3-(*trans*-4-Cyclohexylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido)phenyl)-2-methylfuran-3-carboxylic acid methyl ester

20



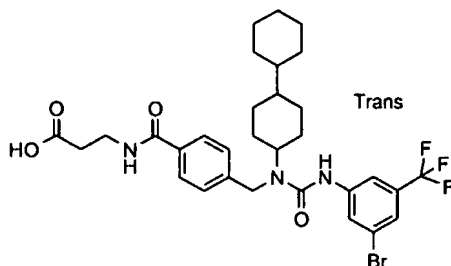
^1H NMR ($\text{DMSO}-d_6$): δ 0.70 -1.25 (m, 10H), 1.41 (q, 2H), 1.66 (m, 8H), 2.47 (m, 2H), 3.78 (s, 3H), 4.08 (m, 1H), 4.62 (s, 2H), 7.02 (s, 1H), 7.21- 7.38 (m, 4H), 7.43 (d, 2H), 7.75 (d, 2H), 7.81 (s, 1H), 8.45 (s, 1H).

25

MS (APCI, pos.): 644.3 (M+1).

EXAMPLE 393 (general procedure (P))

- 5 3-{4-[1-(*trans*-4-Cyclohexylcyclohexyl)-3-(3-bromo-5-trifluoromethylphenyl)ureidomethyl]-benzoylamino}propionic acid

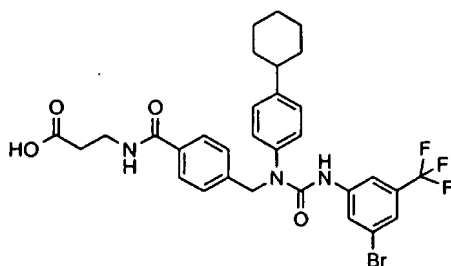


- ¹H NMR (DMSO-*d*₆): δ 0.62 - 1.25 (m, 10H), 1.39 (q, 2H), 1.65 (m, 8H), 2.40 (m, 2H), 3.32 (q, 2 H), 4.04 (m, 1H), 4.60 (s, 2H), 7.31 (d, 2H), 7.46 (s, 1H), 7.75 (d, 2H), 7.93 (s, 1H), 8.08 (s, 1H), 8.45 (s, 1H), 8.83 (s, 1 H).

MS (APCI, pos.): 652.2, 654.1 (M+1).

- 15 EXAMPLE 394 (general procedure (P))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3-bromo-5-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid

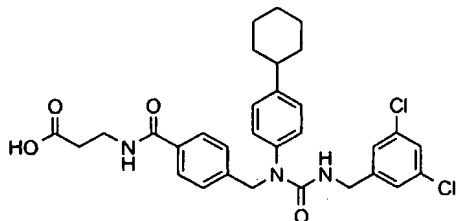


- ¹H NMR (DMSO-*d*₆): δ 1.38 (m, 6H), 1.79 (m, 5H), 2.48 (m, 2 H) 4.96 (s, 2H), 7.22 (m, 4H), 7.36 (d, 2H), 7.50 (s, 1H), 7.77 (d, 2H), 7.94 (s, 1 H), 8.09 (s, 1H), 8.50 (s, 1H), 8.71 (s, 1 H).

MS (APCI, pos.): 646.2, 648.2 (M+1).

EXAMPLE 395 (general procedure (P))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorobenzyl)ureidomethyl]benzoylamino}propionic acid



5

Step A:

To a solution of D-NH₂ (eg. 3,5-dichlorobenzylamine) (1.13 mmol) in acetonitrile (10 mL) was added *N,N'*-disuccinimidylcarbonate (360 mg, 1.13 mmol). The reaction mixture was stirred at room temperature for 4 hours.

10

Step B:

The intermediate 3-{4-[(4-cyclohexylphenylamino)methyl]benzoylamino} propionic acid ethyl ester (1.13 mmol) and diisopropylethylamine (440 mg, 3.42 mmol) were added to the reaction mixture and the reaction mixture was heated at 75°C overnight and concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1N HCl (2 x), brine (3 x), dried over MgSO₄, filtered and concentrated. The material was introduced into a silica gel column and eluted with ethyl acetate/hexane (20/80).

15

Step C:

The product from step B (150 mg, 0.250 mmol) was dissolved in methanol (20 mL) and 2 M LiOH (20 mL) was added. The reaction was stirred for 30 minutes and concentrated. The residue was introduced into a silica gel column and eluted with ethyl acetate. Recrystallisation from ethyl ether/dichloromethane afforded the title compound as a beige solid (35 mg, 25% yield).

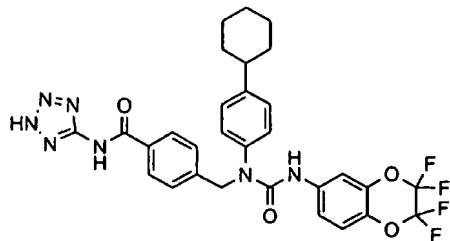
25

¹H NMR (DMSO-*d*₆): δ 1.10-1.34 (m, 6H), 1.70-1.78 (m, 5H), 2.45 (t, 2H), 3.44 (qt, 2H), 4.21 (d, 2H), 4.84 (s, 2H), 6.55 (t, 1H), 7.08 (d, 2H), 7.19-7.21 (m, 6H), 7.44 (s, 1H), 7.74 (d, 2H), 8.45 (t, 1H), 12.10 (brd s, 1H).

30 MS (APCI, pos): 582.1, 584.2.

EXAMPLE 396 (general procedure (P))

4-[1-(4-Cyclohexylphenyl)-3-(2,2,3,3-tetrafluoro-2,3-dihydrobenzo[1,4]dioxin-6-yl)ureido-methyl]-N-(2H-tetrazol-5-yl)benzamide



5

To a solution of 2,2,3,3-tetrafluoro-6-amino-2,3-dihydrobenzo[1,4]dioxine (120 mg, 0.53 mmol) in acetonitrile (10 mL) was added *N,N'*-disuccinimidylcarbonate (130 mg, 0.53 mmol). After stirring the solution for 4 hours at room temperature, 4-[(4-cyclohexylphenylamino)-methyl]-*N*-(1*H*-tetrazol-5-yl)benzamide (200 mg, 0.53 mmol) and diisopropylethylamine (210 mg, 1.59 mmol) were added. The reaction mixture was heated at 75 °C overnight and concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1N HCl (2 x), brine (3 x), dried over MgSO₄, filtered and concentrated. The material was introduced into a silica gel column and eluted with MeOH/ethyl acetate (5/95). The crude product was then recrystallized from ethyl acetate/hexane to afford the title compound as a white-beige powder (12 mg, 0.019 mmol).

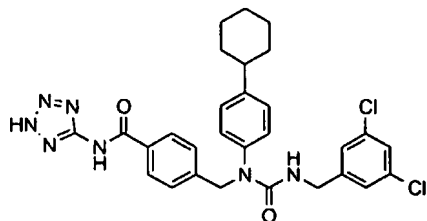
¹H NMR (DMSO-*d*₆): δ 1.36 (m, 6H), 1.78 (m, 5H), 4.99 (s, 2H), 7.21 (m, 4H), 7.33 (s, 2H), 7.45 (d, 2H), 7.63 (s, 1H), 8.01 (s, 2H), 8.57 (s, 1H), 12.20 (brd s, 1H), 16.00 (brd s, 1H).

MS (APCI, pos): 626.2, 627.2.

20

EXAMPLE 397 (general procedure (P))

4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorobenzyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



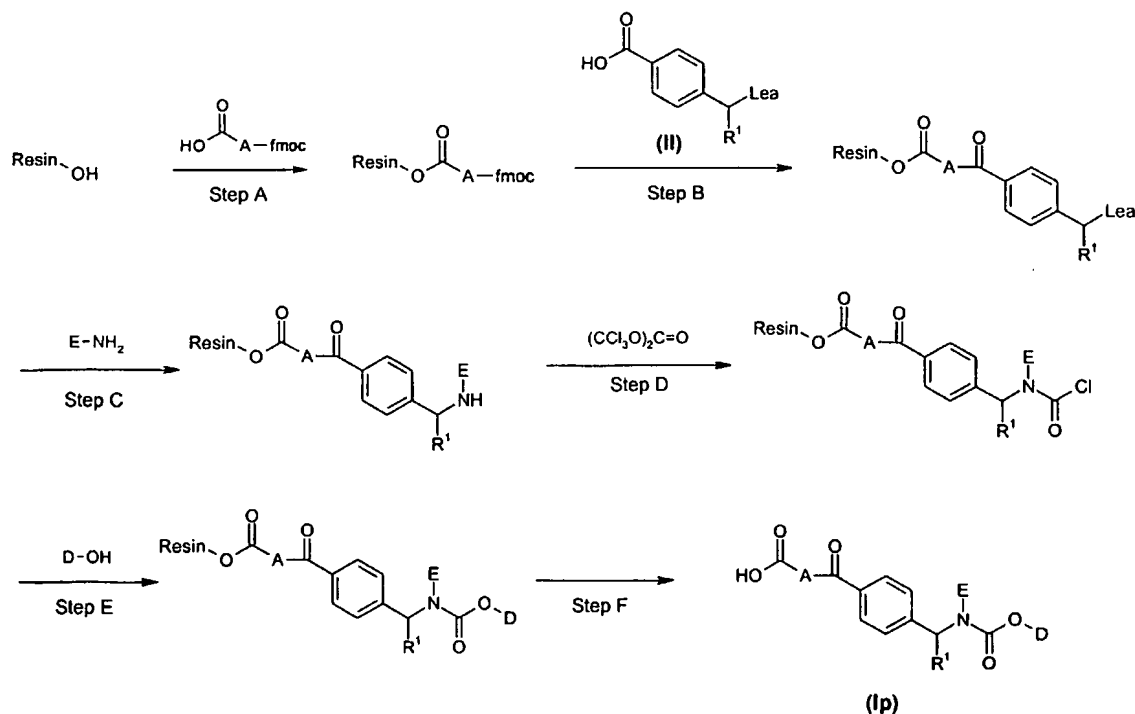
25

To a solution of 3,5-dichlorobenzylamine (200 mg, 1.14 mmol) was added *N,N'*-disuccinimidylcarbonate (360 mg, 1.13 mmol). After stirring the solution for 4 hours at room temperature, tetrazolylaminoamidobenzylaniline (420 mg, 1.13 mmol) and diisopropylethylamine (440 mg, 3.42 mmol) were added. The reaction was heated at 75 °C overnight and concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1N HCl (2 x), brine (3 x), dried over MgSO₄, filtered and concentrated. The title compound was purified by preparatory HPLC.

¹H NMR (DMSO-*d*₆): δ 11.22 (m, 6H), 1.71 (m, 5H), 4.24 (s, 2H), 4.90 (s, 2H), 6.64 (t, 1H), 7.13 (d, 2H), 7.23 (d, 2H), 7.27 (s, 2H), 7.39 (d, 2H), 7.45 (s, 1H), 8.04 (d, 2H), 12.29 (brd s, 1H), 16.00 (brd s, 1H).

MS (APCI, pos): 580.0.

15 General procedure (Q) for the solid phase synthesis of compounds of the general formula (Ip):

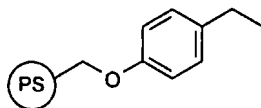


20 wherein

A, R¹, E and D are as defined for formula (Ia),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl, and

- 5 Resin denotes a polystyrene resin with a linker such as the Wang linker:



wherein PS denotes polystyrene.

10

Step A, Step B and Step C are performed as described under general procedure (A).

Alternatively, the resin can be a polystyrene resin with a 2-chlorotrityl linker. In this case, step A is performed as described in eg general procedure (L) or general procedure (V).

15

Step D:

The reaction is performed by stirring resin bound intermediate obtained as described in step C with bistrichloromethyl carbonate (3.3 equivalents). The reaction is carried out in solvents such as dichloromethane, 1,2-dichloroethane or toluene, containing 10 equivalents of a base such as diisopropylethylamine, triethylamine, dicyclohexylamine and the like. The reaction is performed between 0°C and 40°C, preferably between 0°C and 20°C. When the reaction is complete (1-3 h), excess of reagent is removed by filtration. The resin is then washed with dichloromethane and dried in vacuo to leave the resin bound chlorocarbamoyl derivatized intermediate.

25

Step E:

The reaction is performed by stirring resin bound chlorocarbamoyl derivatized intermediate as obtained in step D, with a 10-20 molar excess of alcohols of the type D-OH in the presence of an equal molar excess of base such as diisopropylethylamine, triethylamine, dicyclohexylamine, diazabicycloundecene, or preferably [2.2.2]-diazabicyclooctane. The reaction is carried out in solvents such as DMF, N-methyl-2-pyrrolidone, dichloromethane, 1,2-dichloroethane, THF, toluene or mixtures of one or more of these. The reaction is performed between 0°C and 120°C, preferably at 25°C. When the reaction is completed (12-16 hours) ex-

30

cess of reagent is removed by filtration. The resin is then washed with the solvent used during the reaction followed by several washes with dichloromethane. The resin is dried in vacuo to leave the resin bound carbamate.

5 Step F:

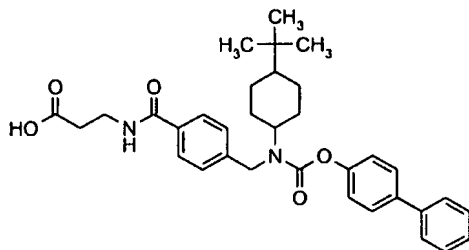
The reaction is known (The combinatorial Index, Ed. Bunin, B.A. 1998, Academic Press, p. 21) and is generally performed by stirring resin bound intermediate with a 5-95% solution of TFA in dichloromethane. The reaction is performed between 0°C and 40°C, preferably at 25°C. When the reaction is complete, the product is removed by filtration. The resin is successively washed with the solvent used during the reaction, optionally containing TFA. The product and the washings are collected, and the solvent is removed in vacuo.

Specific examples illustrating the preparation of compounds of the general formula (Ip) according to the invention are provided below.

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EXAMPLE 398 (general procedure (Q))

3-(4-(((Biphenyl-4-yloxy-carbonyl)-(4-*tert*-butylcyclohexyl)amino)methyl)benzoylamino)-propionic acid



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Step D: Resin bound 3-{4-[1-(4-*tert*-butylcyclohexyl)-*N*-(chlorocarbonyl)aminomethyl]-benzoylamino}propionic acid

Resin bound 3-{4-[1-(4-*tert*-butylcyclohexyl)aminomethyl]benzoylamino}propionic acid (100 mg, 0.1 mmol) as prepared according to step C under general procedure A was suspended in dichloromethane for 1 hour. Solvent was removed by filtration, and a mixture of bis(2-chloromethyl) carbonate (89 mg, 0.3 mmol) and diisopropylethylamine (175 μ L, 1.0 mmol) in dichloromethane (1.0 mL) was added. The mixture was stirred for 90 min. at room temperature. Excess of reagents were removed by filtration, and the resin was subsequently washed with dichloromethane (4 x). The resin was dried in vacuo to leave 105 mg of resin bound

3-{4-[1-(4-*tert*-butylcyclohexyl)-*N*-(chlorocarbonyl)aminomethyl]benzoylamino}propionic acid.

Step E: Resin bound 3-(4-[[[(biphenyl-4-yloxy)carbonyl]-(4-*tert*-butylcyclohexyl)amino]methyl]-benzoylamino}propionic acid

To the resin (50 mg, 0.05 mmol) prepared in step D was added a solution of (85 mg; 0.5 mmol) biphenyl-4-ol, and (2.2.2)-diazabicyclooctane (56 mg; 0.5 mmol) in DMF (1.0 mL). The mixture was stirred at room temperature overnight. Solvent was removed, and the resin was washed with DMF (3 x) followed by dichloromethane (10 x). The resin was dried *in vacuo* to leave 65 mg of resin bound 3-(4-[[[(biphenyl-4-yloxy)carbonyl]-(4-*tert*-butylcyclohexyl)amino]methyl]benzoylamino}propionic acid

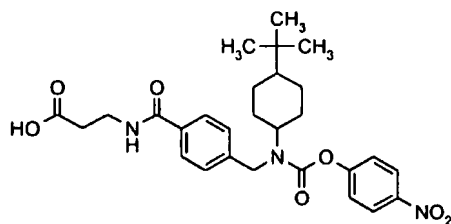
Step F: 3-(4-[[[(Biphenyl-4-yloxy)carbonyl]-(4-*tert*-butylcyclohexyl)amino]methyl]-benzoylamino}propionic acid

To the resin obtained above was added 2 mL of 50% of TFA in dichloromethane. After stirring for 30 min. at 25°C, the solvent was removed by filtration. The resin was washed twice with 50% of TFA in dichloromethane, and the combined filtrate and washings were evaporated to dryness by speed vacuum centrifugation, to leave the title material as a light coloured oil. The product was characterised by analytical HPLC-MS and NMR.

¹H NMR (DMSO): δ 8.44 (s, 1H); 8.35 (s, 1H); 7.78 (d, 2H); 7.45 (d, 2H); 7.38 (d, 2H); 7.34 (d, 2H); 6.94 (m, 5H); 4.60 (s, 2H); 0.81 (s, 9H).

EXAMPLE 399 (general procedure (Q))

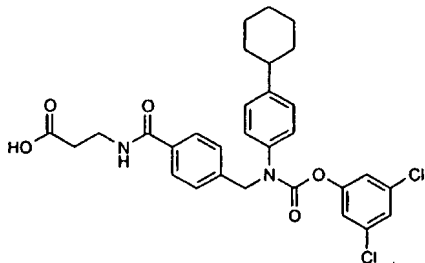
3-(4-[[[(4-*tert*-Butylcyclohexyl)-(4-nitrophenoxy)carbonyl]amino]methyl]benzoylamino}propionic acid



¹H NMR (DMSO): δ 8.40 (t, 1H); 8.25 (d, 2H); 7.82 (d, 2H); 7.78 (d, 2H); 7.44 (d, 2H); 4.61 (s, 2H); 0.85 (s, 9H).

EXAMPLE 400 (general procedure (Q))

3-(4-((4-Cyclohexylphenyl)-(3,5-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

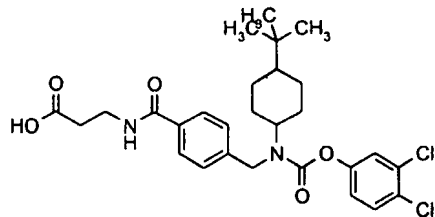


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¹H NMR (DMSO): δ 8.57 (t, 1H); 7.88 (d, 2H); 7.60 (s, 1H); 7.50 (m, 4H); 7.40 (d, 2H); 7.29 (d, 2H).

EXAMPLE 401 (general procedure (Q))

10 3-(4-((4-*tert*-Butylcyclohexyl)-(3,4-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

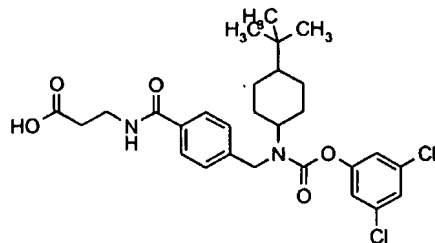


15

¹H NMR (DMSO): δ 8.58 (t, 1H); 7.91 (d, 2H); 7.73 (d, 1H); 7.58 (d, 1H); 7.48 (d, 2H); 7.22 (d, 1H).

EXAMPLE 402 (general procedure (Q))

3-(4-((4-*tert*-Butylcyclohexyl)-(3,5-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

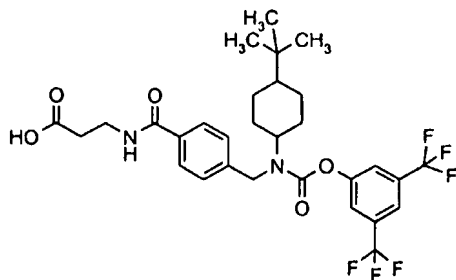


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¹H NMR (DMSO): δ 8.59 (t, 1H); 7.90 (d, 2H); 7.55 (m, 4H); 7.35 (s, 1H).

EXAMPLE 403 (general procedure (Q))

3-(4-(((3,5-Bis(trifluoromethyl)phenoxy)carbonyl)-(4-*tert*-butylcyclohexyl)amino)methyl)-benzoylamino)propionic acid

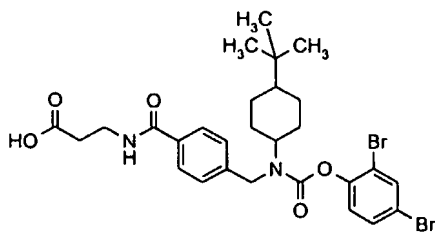


5

^1H NMR (DMSO): δ 8.58 (t, 1H); 8.12 ((d, 1H); 8.05 (d, 2H); 7.90 (m, 2H); 7.55 (m, 2H).

EXAMPLE 404 (general procedure (Q))

10 3-(4-(((4-*tert*-Butylcyclohexyl)-(2,4-dibromophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

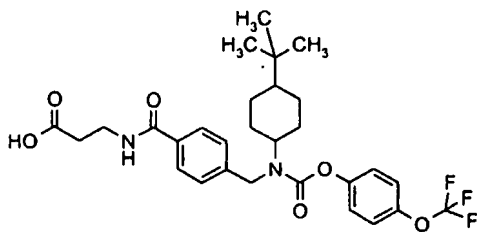


^1H NMR (DMSO): δ 8.04 (s, 1H); 7.91 (d, 2H); 7.71 (d, 1H); 7.52 (d, 2H); 7.37 (m, 1H).

15

EXAMPLE 405 (general procedure (Q))

3-(4-(((4-*tert*-Butylcyclohexyl)-(4-trifluoromethoxyphenoxy)carbonyl)amino)methyl)benzoylamino)propionic acid

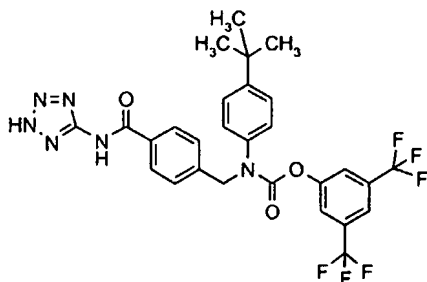


20

^1H NMR (DMSO): δ 8.59 (t, 1H); 7.91 (d, 2H); 7.47 (dd, 4H); 7.30 (d, 2H).

EXAMPLE 406 (general procedure (Q))

(4-*tert*-Butylphenyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 3,5-bis(trifluoromethyl)phenyl ester

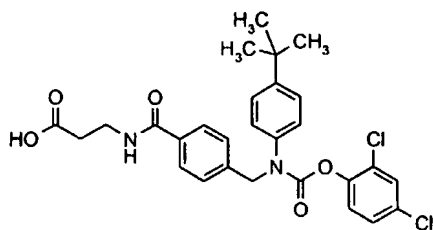


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¹H NMR (DMSO): δ 8.17 (s, 2H); 8.11 (s, 1H); 7.67 (d, 2H); 7.51 (m, 4H); 5.18 (s, 2H).

EXAMPLE 407 (general procedure (Q))

10 3-(4-[(4-*tert*-Butylphenyl)-(2,4-dichlorophenoxy)carbonyl]amino)methyl)benzoylamino)-propionic acid

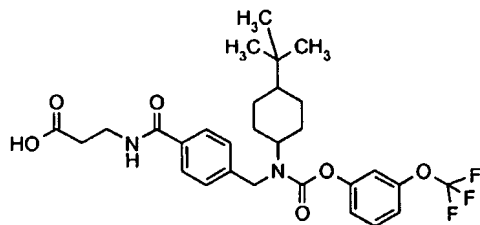


15

¹H NMR (DMSO): δ 8.58 (t, 1H); 7.89 (d, 2H); 7.84 (s, 1H); 7.56 (dd, 1H); 7.48 (m, 5H); 7.39 (d, 2H); 5.06 (s, 2H).

EXAMPLE 408 (general procedure (Q))

3-(4-[(4-*tert*-Butylcyclohexyl)-(3-trifluoromethoxyphenoxy)carbonyl]amino)methyl)benzoylamino)propionic acid

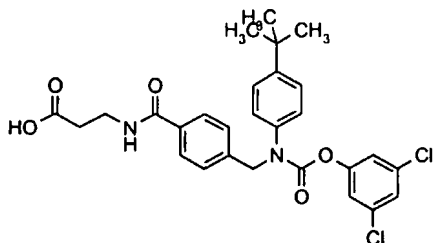


20

^1H NMR (DMSO): δ 8.59 (t, 1H); 7.91 (d, 2H); 7.69 (t, 1H); 7.47 (dd, 4H); 7.32 (m, 1H); 7.27 (m, 1H); 7.20 (m, 1H).

EXAMPLE 409 (general procedure (Q))

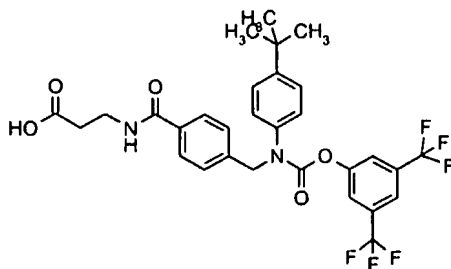
- 5 3-(4-(((4-*tert*-Butylphenyl)-(3,5-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid



- 10 ^1H NMR (DMSO): δ 8.60 (t, 1H); 7.88 (d, 2H); 7.60 (s, 1H); 7.50 (m, 4H); 7.46 (d, 2H); 7.43 (d, 2H); 5.08 (s, 2H).

EXAMPLE 410 (general procedure (Q))

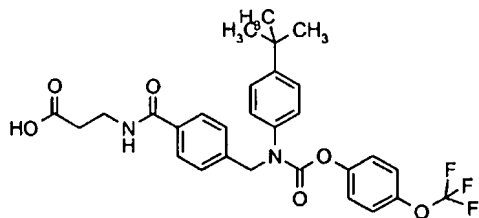
- 3-(4-(((3,5-Bis(trifluoromethyl)phenoxy)carbonyl)-(4-*tert*-butylphenyl)amino)methyl)benzoylamino)propionic acid



- 15 ^1H NMR (DMSO): δ 8.60 (t, 1H); 8.15 (s, 2H); 8.10 (s, 1H); 7.89 (d, 2H); 7.55 (d, 2H); 7.49 (s, 4H); 5.11 (s, 1H).

EXAMPLE 411 (general procedure (Q))

3-(4-(((4-*tert*-Butylphenyl)-(4-trifluoromethoxyphenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid



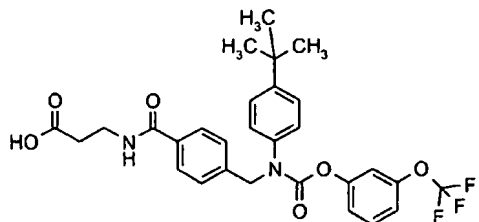
5

¹H NMR (DMSO): δ 8.59 (t, 1H); 7.88 (d, 2H); 7.48 (m, 6H); 7.39 (m, 4H); 5.09 (s, 2H).

EXAMPLE 412 (general procedure (Q))

3-(4-(((4-*tert*-Butylphenyl)-(3-trifluoromethoxyphenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

10

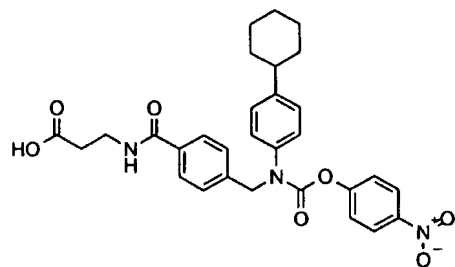


¹H NMR (DMSO): δ 8.59 (t, 1H); 7.88 (d, 2H); 7.61 (t, 1H); 7.48 (m, 4H); 7.39 (m, 5H); 5.09 (s, 2H).

15

EXAMPLE 413 (general procedure (Q))

3-(4-(((4-Cyclohexylphenyl)-(4-nitrophenoxy)carbonyl)amino)methyl)benzoylamino)propionic acid

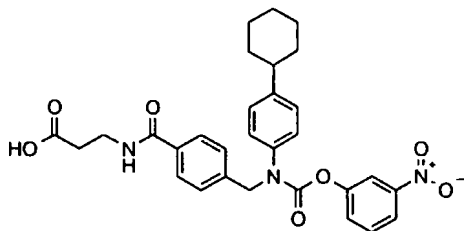


20

¹H NMR (DMSO): δ 8.57 (t, 1H); 8.36 (d, 2H); 7.88 (d, 2H); 7.55 (d, 2H); 7.49 (d, 2H); 7.40 (d, 2H); 7.31 (d, 2H); 5.09 (s, 2H).

EXAMPLE 414 (general procedure (Q))

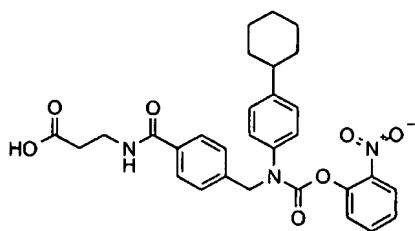
5 3-(4-(((4-Cyclohexylphenyl)-(3-nitrophenoxy)carbonyl)amino)methyl)benzoylamino)propionic acid



10 ¹H NMR (DMSO): δ 8.57 (t, 1H); 8.19 (m, 2H); 7.88 (d, 2H); 7.76 (dd, 2H); 7.51 (d, 2H); 7.41 (d, 2H); 7.31 (d, 2H); 5.10 (s, 2H).

EXAMPLE 415 (general procedure (Q))

3-(4-(((4-Cyclohexylphenyl)-(2-nitrophenoxy)carbonyl)amino)methyl)benzoylamino)propionic acid

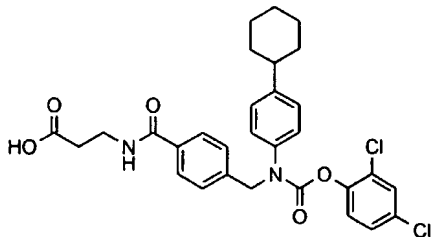


15

¹H NMR (DMSO): δ 8.59 (t, 1H); 8.21 (d, 1H); 7.89 (m, 3H); 7.63-7.31 (m, 7H); 5.05 (s, 2H).

EXAMPLE 416 (general procedure (Q))

3-(4-[[[(4-Cyclohexylphenyl)-(2,4-dichlorophenoxy)carbonyl]amino]methyl]benzoylamino)-propionic acid

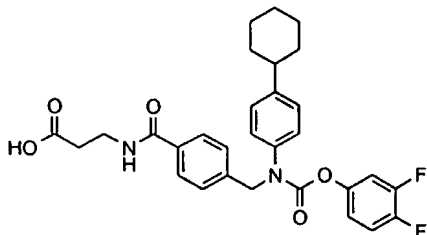


5

^1H NMR (DMSO): δ 8.58 (t, 1H); 7.88 (d, 2H); 7.83 (s, 1H); 7.57-7.45 (m, 5H); 7.38 (d, 2H); 7.31 (d, 2H); 5.06 (s, 2H).

EXAMPLE 417 (general procedure (Q))

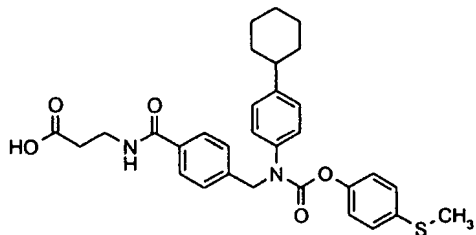
10 3-(4-[[[(4-Cyclohexylphenyl)-(3,4-difluorophenoxy)carbonyl]amino]methyl]benzoylamino)-propionic acid



15 ^1H NMR (DMSO): δ 8.58 (t, 1H); 7.87 (d, 2H); 7.55-7.45 (m, 4H); 7.38 (d, 2H); 7.29 (d, 2H); 7.13 (m, 1H); 5.07 (s, 2H).

EXAMPLE 418 (general procedure (Q))

3-(4-[[[(4-Cyclohexylphenyl)-(4-methylsulfanylphenoxy)carbonyl]amino]methyl]benzoylamino)-propionic acid

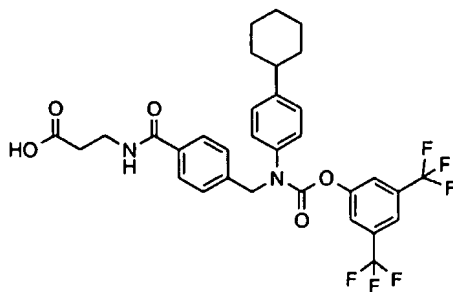


20

¹H NMR (DMSO): δ 8.58 (t, 1H); 7.87 (d, 2H); 7.46 (d, 2H); 7.35 (m, 4H); 7.29 (d, 2H); 7.18 (d, 2H); 5.07 (s, 2H).

EXAMPLE 419 (general procedure (Q))

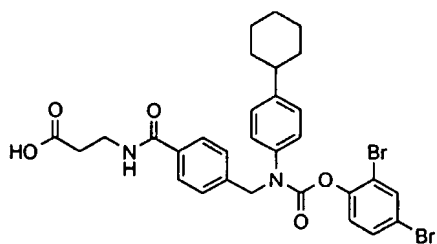
- 5 3-(4-((3,5-Bis(trifluoromethyl)phenoxy)carbonyl)-(4-cyclohexylphenyl)amino)methyl)-benzoylamino)propionic acid



- 10 ¹H NMR (DMSO): δ 8.58 (t, 1H); 8.14 (s, 2H); 8.10 (s, 1H); 7.88 (d, 2H); 7.53 (d, 2H); 7.47 (d, 2H); 7.31 (d, 2H); 5.10 (s, 2H).

EXAMPLE 420 (general procedure (Q))

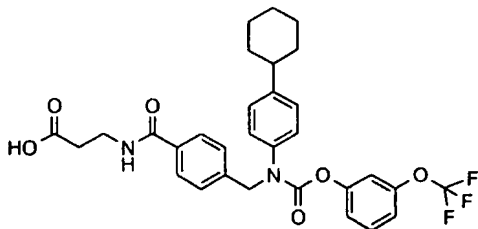
- 15 3-(4-((4-Cyclohexylphenyl)-(2,4-dibromophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid



¹H NMR (DMSO): δ 8.57 (t, 1H); 8.04 (s, 1H); 7.88 (d, 2H); 7.72 (d, 1H); 7.50 (bd, 2H); 7.42 (m, 3H); 7.38 (d, 2H); 5.05 (s, 2H).

EXAMPLE 421 (general procedure (Q))

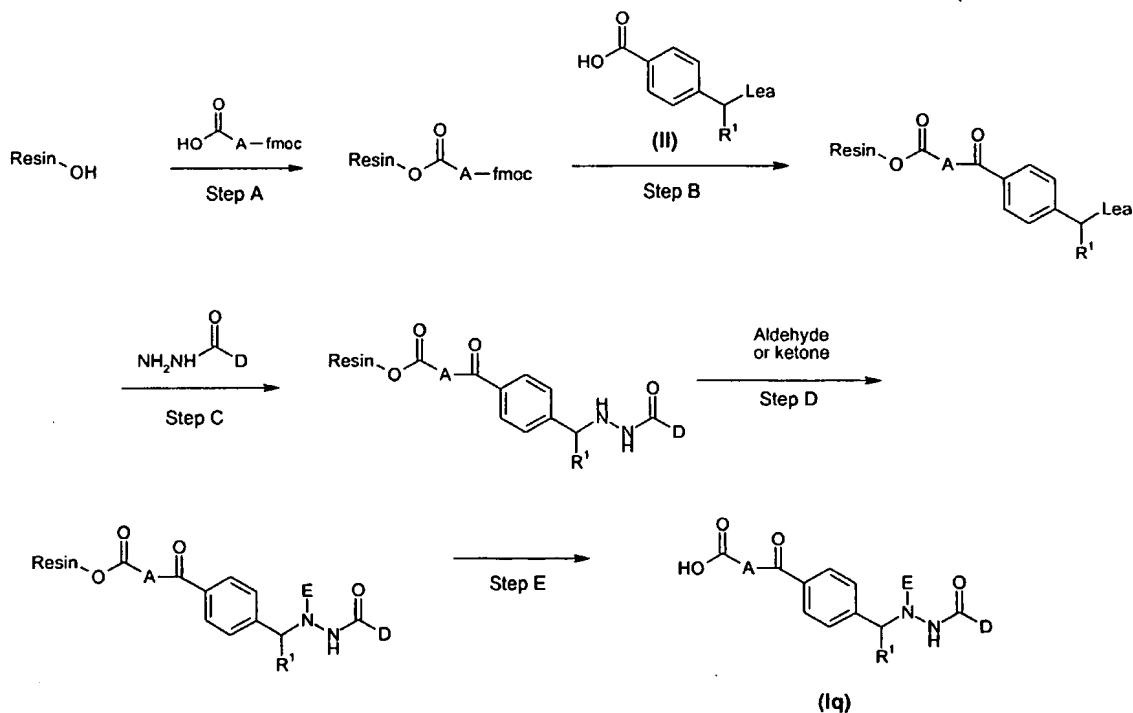
3-(4-(((4-Cyclohexylphenyl)-(3-trifluoromethoxyphenoxy)carbonyl)amino)methyl)benzoyl-amino)propionic acid



5

^1H NMR (DMSO): δ 8.59 (t, 1H); 7.88 (d, 2H); 7.62 (t, 1H); 7.49 (d, 2H); 7.41-7.30 (m, 7H); 5.09 (s, 2H).

General procedure (R) for the solid phase synthesis of compounds of the general formula

10 (Iq):

wherein

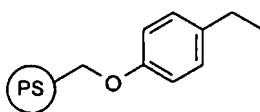
15

A, R¹, E and D are as defined for formula (Ia),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:

5



wherein PS denotes polystyrene.

10 Step A and Step B are performed as described under general procedure A.

Step C:

The reaction is performed by stirring the resin bound intermediate obtained in step B with 10 - 20 molar excess of hydrazide. The nucleophilic displacement is carried out in solvents such as DMSO, DMF, *N*-methyl-2-pyrrolidone or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably between 60°C and 80°C. When the reaction is complete, excess of reagent is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

20

Step D:

The reductive amination is generally known (The combinatorial Index, Ed. Bunin, B.A. 1998, Academic Press, p. 167) and is performed by stirring the resin bound hydrazide intermediate obtained in step C with an excess of aldehyde or ketone at low pH (by addition of an acid, such as acetic or formic acid). The reaction is carried out in solvents such as THF, DMF, *N*-methyl-2-pyrrolidone, ethanol, methanol, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or mixtures of two or more of these. As reducing reagent sodium cyanoborohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. When the reaction is complete, excess of reagents are removed by filtration and the resin is washed several times with the solvent used during the reaction. The resin bound product can be further dried and analyzed.

30

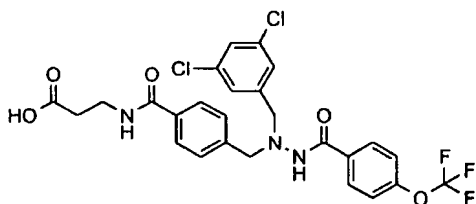
Step E:

The cleavage reaction is known (The combinatorial Index, Ed. Bunin, B.A. 1998, Academic Press, p. 21) and is generally performed by stirring resin bound intermediate with a 5-95% solution of TFA in dichloromethane. The reaction is performed between 0°C and 40°C, preferably at 25°C. When the reaction is complete, the product is removed by filtration. The resin is successively washed with the solvent used during the reaction, optionally containing TFA. The product and the washings are collected, and solvent removed in vacuo.

Specific examples illustrating the preparation of compounds of the general formula (Iq) according to the invention are provided below.

EXAMPLE 422 (general procedure (R))

3-{4-[N-(3,5-Dichlorobenzyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}-propionic acid



Step C: Resin bound 3-{4-[N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}-propionic acid

Resin bound 3-[4-(bromomethyl)benzoylamino]propionic acid (50 mg; 0.05 mmol) prepared as described under general procedure (A), was suspended in DMSO for an hour. Solvent was removed by filtration, and a solution of 4-trifluoromethoxybenzoylhydrazide (110 mg; 0.5 mmol) in DMSO (1 mL) was added. The reaction mixture was stirred at 80°C for 16 hours, before removing excess of reagent by filtration. The resin was then washed with DMF (3 x 1 mL) followed by dichloromethane (3 x 1 mL) to afford 50 mg of resin bounded 3-{4-[N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid.

Step D: Resin bound 3-{4-[N-(3,5-Dichlorobenzyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid

To resin bound intermediate obtained as above was added a mixture of 3,5-dichloro-benzaldehyde (175 mg, 1.0 mmol) and acetic acid (0.1 mL) in trimethyl orthoformate (1.0 mL). The resin was stirred for 2 h at ambient temperature. Sodium cyanoborohydride (63 mg, 1.0

mmol) dissolved in DMF (1.0 mL) was then added and the mixture was left stirred at room temperature for 16 h. Excess of reagent was removed by filtration, and the resin was washed with DMF (3 x 1 mL) followed by dichloromethane (8 x).

5 Step E: 3-{4-[N-(3,5-Dichlorobenzyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-benzoylamino}propionic acid

To the resin obtained above was added 2 mL of 50% of TFA in dichloromethane. After stirring for 30 min. at 25°C, the solvent was removed by filtration. The resin was washed twice with 50% of TFA in dichloromethane, and the combined filtrate and washings were taken to
10 dryness by speed vacuum centrifugation, to leave the title compound as a light coloured oil. The product was characterised by analytical LC-MS and NMR.

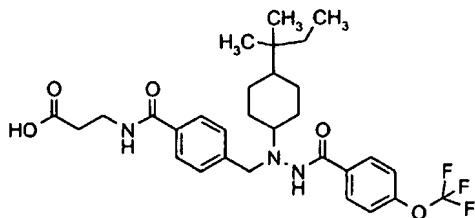
¹H NMR (DMSO): δ 9.62 (s, 1H); 8.47 (t, 1H); 7.80 (d, 2H); 7.70 (d, 2H); 7.52 (s, 2H); 7.49 (d, 2H); 7.42 (d, 2H); 4.22 (s, 2H); 4.16 (s, 2H).

15

HPLC-MS (Method B): m/z = 584.2 (M+1). R_t = 7.11 min.

EXAMPLE 423 (general procedure (R))

20 3-{4-[N-[4-(1,1-Dimethylpropyl)cyclohexyl]-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-benzoylamino}propionic acid



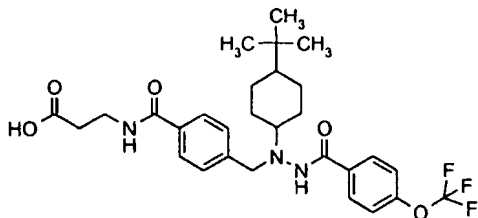
¹H NMR (DMSO): δ 9.21 (s, 1H); 8.42 (s, 1H); 7.73 (dd, 4H); 7.49 (d, 2H); 7.40 (d, 2H); 4.11 (s, 2H); 1.20 (t, 3H); 1.04 (q, 2H); 0.74 (s, 6H).

25

HPLC-MS (Method B): m/z = 578.2 (M+1). R_t = 7.74 min.

EXAMPLE 424 (general procedure (R))

3-{4-[N-(4-*tert*-Butylcyclohexyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid



5

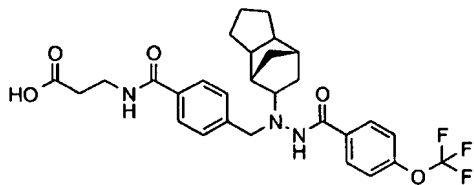
¹H NMR (DMSO): δ 9.20 (s, 1H); 8.42 (t, 1H); 7.72 (dd, 4H); 7.50 (d, 2H); 7.40 (d, 2H); 4.14 (s, 2H); 0.84 (s, 9H).

HPLC-MS (Method B): m/z = 564.4 (M+1). R_t = 7.47 min.

10

EXAMPLE 425 (general procedure (R))

3-{4-[N-(Octahydro-4,7-methanoinden-5-yl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid



15

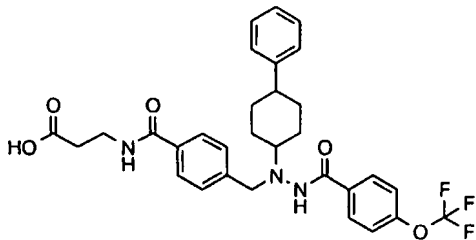
¹H NMR (DMSO): δ 9.29 (s, 1H); 8.46 (t, 1H); 7.75 (d, 2H); 7.70 (d, 2H); 7.47 (d, 2H); 7.40 (d, 2H).

HPLC-MS (Method B): m/z = 560.4 (M+1). R_t = 7.51 min.

20

EXAMPLE 426 (general procedure (R))

3-{4-[N-(4-Phenylcyclohexyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}-propionic acid



5

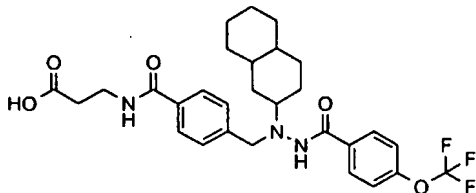
^1H NMR (DMSO): δ 9.38 (s, 1H); 8.46 (t, 1H); 7.76 (d, 2H); 7.71 (d, 2H); 7.53 (d, 2H); 7.40 (d, 2H); 7.18-7.43 (m, 5H); 4.18 (s, 2H).

HPLC-MS (Method B): m/z = 584.4 ($M+1$). R_t = 7.01 min.

10

EXAMPLE 427 (general procedure (R))

3-{4-[N-(Decahydronaphthalen-2-yl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid

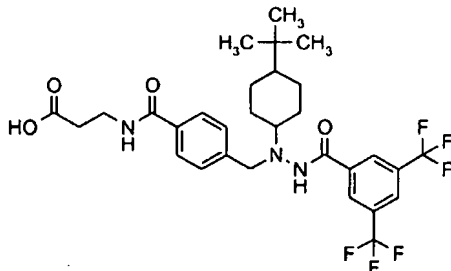


15

^1H NMR (DMSO): δ 9.23 (s, 1H); 8.42 (t, 1H); 7.72 (dd, 4H); 7.50 (d, 2H); 7.42 (d, 2H); 4.15 (s, 2H).

HPLC-MS (Method B): m/z = 562.4 ($M+1$). R_t = 7.24 min.

20

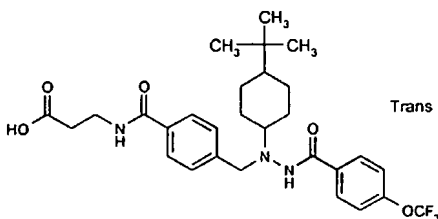
EXAMPLE 428 (general procedure (R))**3-{4-[N'-(3,5-Bis(trifluoromethyl)benzoyl)-N-(4-*tert*-butylcyclohexyl)hydrazinomethyl]benzoylamino}propionic acid**

5

^1H NMR (DMSO): δ 9.55 (s, 1H); 8.46 (t, 1H); 8.26 (s, 2H); 7.75 (d, 2H); 7.50 (d, 2H); 4.18 (s, 2H); 0.85 (s, 9H).

HPLC-MS (Method B): m/z = 616.4 (M+1). R_t = 8.11 min.

10

EXAMPLE 429**3-{4-[N-(*trans*-4-*tert*-Butylcyclohexyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid**

15

To an ice-cooled solution of hydrazine hydrate (16 mL, 25% (w/w), 125 mmol) in THF (100 mL) was added a solution of 4-trifluoromethoxybenzoyl chloride (4.3 g, 19.2 mmol) in THF (50 mL) over 30 min. The solution was stirred for a further 30 min and then diluted with ether (200 mL). The turbid organic solution was then washed with water (3 x 200 mL) and brine (200 mL). After drying (Na_2SO_4), solvent was removed by rotary evaporation. The solid residue was dissolved in ethanol/water (1:1, 200 mL), insoluble material was filtered off, and the filtrate taken to dryness to leave 3.63 g (86%) of pure 4-trifluoromethoxybenzoic acid hydrazide.

20

^1H NMR (DMSO- d_6), 300 MHz: δ 9.90 (s, 1H); 7.92 (d, 2H); 7.45 (d, 2H), 4.52 (bs, 2H).

25

HPLC-MS (Method B): R_t = 4.04 min, m/z = 221 (M+1).

The above 4-trifluoromethoxybenzoic acid hydrazide (3.60 g, 16.3 mmol) and 4-*tert*-butylcyclohexanone (2.52 g, 16.3 mmol) was dissolved in ethanol (150 mL) and the solution was heated to reflux. After 30 min, powdered sodium borohydride (0.96 g, 25.2 mmol) was carefully added, and the mixture stirred for an additional 30 min at reflux. The reaction was cooled to 25°C, and remains of sodium borohydride were quenched by addition of acetic acid (10 mL). The volume of the reaction mixture was reduced to one third by rotary evaporation before adding water (100 mL) and diethyl ether (200 mL). The organic phase was then collected, washed once with brine and dried over anhydrous Na₂SO₄. The organic phase was taken to dryness, and the residual oil purified by column chromatography (silica gel G 60, ethyl acetate/heptane (1:4)) to afford the pure *trans* and *cis* isomers of 4-trifluoromethoxybenzoic acid *N'*-(4-*tert*-butylcyclohexyl)hydrazide.

trans isomer: TLC: R_f = 0.10 ethyl acetate/heptane (1:4).

¹H NMR (DMSO-*d*₆), 300 MHz: δ 10.04 (s, 1H); 7.94 (d, 2H); 7.45 (d, 2H); 4.98 (bs, 1H); 2.65 (m, 1H); 1.06-1.95 (m, 4H); 0.86-1.12 (m, 5H); 0.80 (s, 9H).

cis isomer: TLC: R_f = 0.25 ethyl acetate/heptane (1:4).

¹H NMR (DMSO-*d*₆), 300 MHz: δ 10.02 (s, 1H); 7.96 (d, 2H); 7.45 (d, 2H); 4.89 (bs, 1H); 3.08 (s, 1H); 1.85 (m, 2H); 1.31-1.52 (m, 6H); 0.95 (m, 1H); 0.85 (s, 9H).

trans-3-{4-[*N*-(4-*tert*-Butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid

trans-4-Trifluoromethoxybenzoic acid *N'*-(4-*tert*-butylcyclohexyl)hydrazide (715 mg, 2 mmol) was dissolved in DMSO (8 mL), and added to 3-[4-(bromomethyl)benzoyl]aminopropanoic acid derivatized Wang resin (2.0 g, loading app. 0.5 mmol/g) prepared as described in example 1. The mixture was heated to 80°C for 24 hours, and then cooled. After draining, the resin was washed with DMSO (3 x), DMF (3 x) and dichloromethane (10 x). A 50% TFA/dichloromethane solution (8 mL) was then added, and the mixture was left for 30 min at 25°C. The supernatant was collected, and the resin subsequently washed once with a 50% TFA/dichloromethane solution (8 mL). The combined supernatant and washing were taken to dryness by rotary evaporation, to leave a brown oil. Further purification by column chromatography (silica G60, 400 mesh, 48% ethyl acetate, 48% heptane, 4% acetic acid), and crystallization (ethanol/water) gave the title compound as fine needles.

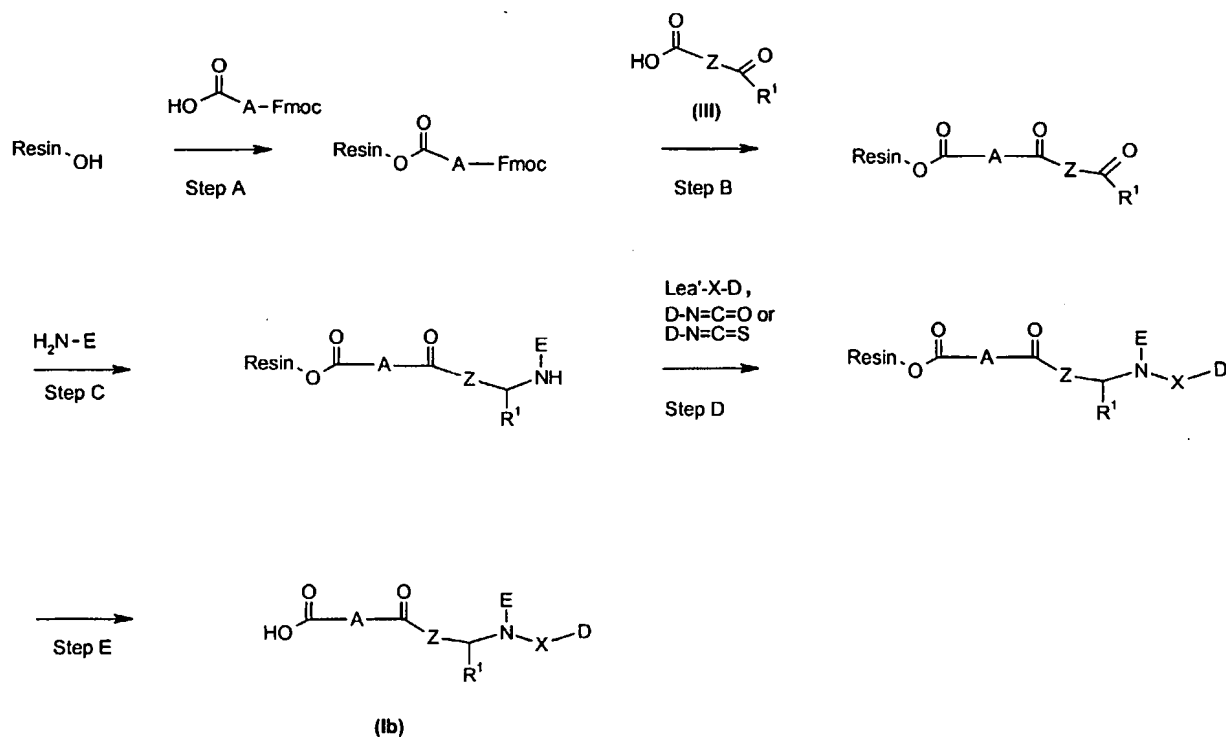
$R_f = 0.15$ ethyl acetate/heptane (1:1).

^1H NMR ($\text{DMSO}-d_6$), 300 MHz: δ 12.18 (s, 1H); 9.20 (s, 1H); 8.42 (t, 1H); 7.74 (d, 2H); 7.72 (d, 2H); 4.47 (d, 2H); 7.38 (d, 2H); 4.12 (s, 2H); 3.42 (dt, 2H); 2.82 (m, 1H); 2.50 (t, 2H); 2.04 (bd, 2H); 1.77 (bd, 2H); 1.24 (m, 2H); 0.96 (m, 3H); 0.82 (s, 9H).

HPLC-MS (Method B): $R_t = 7.57$ min, $m/z = 564$ (M+1).

10 General procedure (S) for the solid phase synthesis of compounds of the general formula (Ib):

Steps B and C are modified compared to general procedure (C) so that step C is a reductive amination of a resin bound aldehyde or ketone:



15

wherein

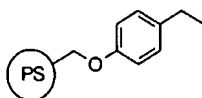
A, Z, R^1 , E and D are as defined for formula (I),

20 X is $-\text{S}(\text{O})_2-(\text{CH}_2)_r-$, $-\text{C}(\text{O})\text{NH}-$ or $-\text{C}(\text{S})\text{NH}-$, wherein r is as defined for formula (I),

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:

5



wherein PS denotes polystyrene.

10 Step B:

The Fmoc protecting group is removed using a solution of 20% piperidine in DMF which is added to the resin and vortexed for 0.5 hours. After draining the resin is washed with DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF.

- 15 The acylation (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) is performed by adding an excess of acid (III) in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling
- 20 reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromotris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a side reaction inhibitor such as 3-
- 25 hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

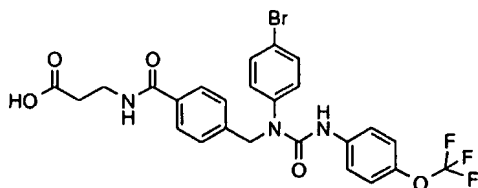
30 Step C:

The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring resin bound aldehyde or ketone with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, *N*-methylpyrrolidinone, methanol, ethanol, DMSO, dichloro-

methane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. As reducing agent sodium cyanoborohydride may be used. The reaction is performed between 20°C and 120°C, preferably at 25°C.

5 EXAMPLE 430 (general procedure (S))

3-{4-[1-(4-Bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



10 ¹H NMR (DMSO): δ 6.52 (2H, d), 7.20 (2H, d), 7.43 (2H, d), 7.77 (2H, d), 8.47 (1H, t).

Step A: Resin bound Fmoc β-alanine

15 150 μmol Fmoc β-alanine was dissolved in 500 μL of a mixture of DMF and diisopropylethylamine (430:70) and added to 50 mg polystyrene resin functionalised with a Wang linker. 200 μmol PyBrOP dissolved in DMF (500 μL) was added. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 3 x 1 mL DMF.

Step B: Resin bound 3-(4-formylbenzoylamino)propionic acid

20 To the above resin bound Fmoc β-alanine was added 1000 μL of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200 μmol 4-formylbenzoic acid (30 mg) and diisopropylethylamine (70 μL) were dissolved in DMF (430 μL) and added to the resin followed by 200 μmol PyBrOP dissolved in DMF (500 μL). The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with DMF (3 x 1 mL) and trimethylorthoformate (1 x 1 mL).

Step C: Resin bound 3-{4-[(4-bromophenylamino)methyl]benzoylamino}propionic acid

30 The above resin bound 3-(4-formylbenzoylamino)propionic acid (50 mg) was treated with a solution of 4-bromoaniline (500 μmol) in a mixture of DMF (500 μL) and trimethylorthoformate (500 μL). Glacial acetic acid (100 μL) was added and the mixture was shaken for 1 hour at 25°C. Sodium cyanoborohydride (750 μmol) suspended in a mixture of DMF and trimethyl-

orthoformate (1:1, 1 mL) was added and the mixture was vortexed at 25°C for 16 hours followed by filtration and washing with a mixture of DMF and water (4:1, 2 x 1 mL) followed by 3 x 1 mL DMF and 2 x 1 mL dichloromethane to afford the desired product.

5 Step D: Resin bound 3-{4-[1-(4-bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

200 µmol 4-trifluoromethoxyphenylisocyanate dissolved in 500 µL dichloromethane was added to the above resin bound 3-{4-[(4-bromophenylamino)methyl]benzoylamino}propionic acid (50 mg). Shaking the mixture for 16 hours at 25°C followed by filtration and washing of
10 the resin with 4 x 1 mL DMF, 2 x 1 mL water, 3 x 1 mL THF and 5 x 1 mL dichloromethane afforded the resin bound title compound.

Step E: 3-{4-[1-(4-Bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

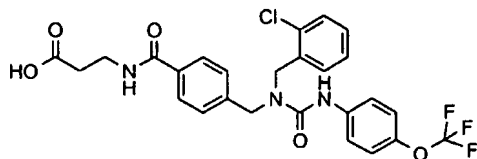
15 The above resin bound 3-{4-[1-(4-bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid (50 mg) was treated with 1 mL 50% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was purified by preparative HPLC to afford the title compound.

20

The following compounds were made according to the general procedure (S):

EXAMPLE 431 (general procedure (S))

25 3-{4-[1-(2-Chlorobenzyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

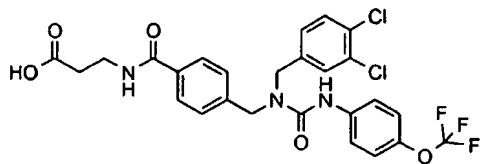


¹H NMR (DMSO): δ 4.63 (2H, s), 4.65 (2H, s), 7.2-7.4 (7H, m), 7.47 (1H, d), 7.61 (2H, d), 7.81 (2H, d), 8.49 (1H, t), 8.90 (1H, s).

.30

EXAMPLE 432 (general procedure (S))

3-{4-[1-(3,4-Dichlorobenzyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

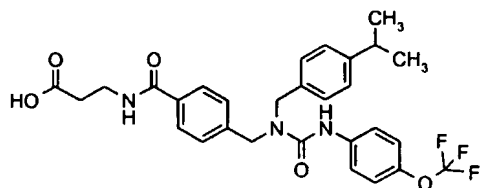


5

¹H NMR (DMSO): δ 8.85 (s, 1H); 8.46 (t, 1H); 7.80 (d, 2H); 7.61 (d, 2H); 7.59 (s, 1H); 7.50 (s, 1H); 7.35 (d, 2H); 7.25 (d, 2H); 7.23 (s, 1H); 4.65 (s, 2H); 4.52 (s, 2H); 3.46 (q, 2H); 2.50 (t, 2H).

10 EXAMPLE 433 (general procedure (S))

3-{4-[1-(4-Isopropylbenzyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

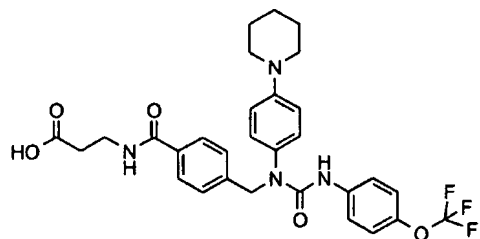


15 ¹H NMR (DMSO): δ 8.80 (s, 1H); 8.51 (t, 1H); 7.82 (d, 2H); 7.60 (d, 2H); 7.30 d, 2H); 7.25 (d, 2H); 7.21 (d, 2H); 7.18 (d, 2H); 4.61 (s, 2H); 4.55 (s, 1H); 3.46 (q, 2H); 1.20 (d, 6H).

EXAMPLE 434 (general procedure (S))

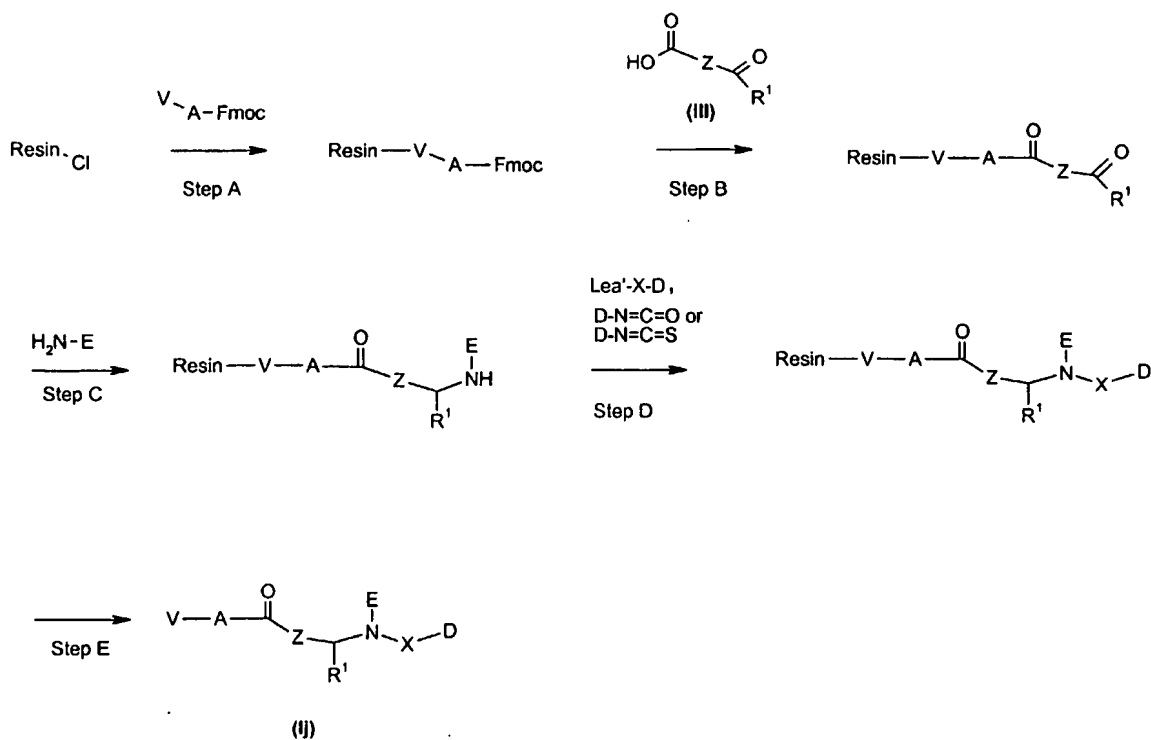
3-{4-[1-(4-Piperidin-1-ylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

20



¹H NMR (DMSO): δ 8.46 (t, 1H); 8.10 (s, 1H); 7.78 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.25 (d, 2H); 7.12 (d, 2H); 7.05 (d, 2H); 4.90 (s, 2H).

General procedure (T) for the solid phase synthesis of compounds of the general formula (II):
Alternatively, the solid support used in general procedure (S) can be a 2-chlorotrityl polystyrene resin.



5

wherein

V, A, Z, R¹, E and D are as defined for formula (I),

10

X is -C(O)NH- or -C(S)NH- and

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy.

15 Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of a nucleophilic Fmoc protected amine (V-A-Fmoc) in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, N-methylpyrrolidinone, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C

20

and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotritylchloride.

5

Step B:

Step B is identical to step B of general procedure (S).

Step C:10

Step C is identical to step C of general procedure (S).

Step D:

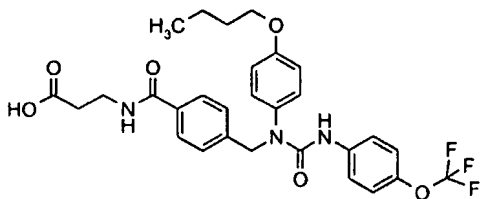
Step D is identical to step D of general procedure (S).

15 Step E:

Step E is identical to step E of general procedure (S).

EXAMPLE 435 (general procedure (T))

3-{4-[1-(4-Butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic
20 acid

Step A: Resin bound Fmoc β-alanine

150 μmol Fmoc β-alanine was dissolved in a mixture of 250 μL dichloromethane, 250 μL
25 DMF and 100 μL diisopropylethylamine and added to 50 mg polystyrene resin functionalized
with a 2-chlorotrityl linker. After shaking the suspension for 4 hours at 25°C, the resin was
isolated by filtration and washed with 2 x 1 mL dichloromethane: metha-
nol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step B: Resin bound 3-(4-formylbenzoylamino)propionic acid

To the above resin bound Fmoc β -alanine was added 500 μ L of a 20% solution of piperidine in DMF. After 30 min of shaking, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200 μ mol 4-formylbenzoic acid (30 mg) and 200 μ mol HOBt (31 mg) dissolved in DMF (500 μ L) were added to the resin followed by 200 μ mol diisopropyl carbodiimide (DIC, 25.2 mg) dissolved in acetonitrile (500 μ L). The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with DMF (3 x 1 mL).

Step C: Resin bound 3-{4-[(4-Butoxyphenylamino)methyl]benzoylamino}propionic acid

The above resin bound 3-(4-formylbenzoylamino)propionic acid (50 mg) was treated with a 0.5 M solution of 4-butoxyaniline (0.25 mmol, 41.25 mg) in a mixture of DMF and trimethyl-orthoformate (1:1, 0.5 mL) and glacial acetic acid (50 μ L) for 1 hour at 25 °C. Sodium cyanoborohydride (250 μ mol, 16 mg) dissolved in a mixture of DMF and methanol (1:1, 0.25 mL) was added, and the mixture was vortexed at 25°C for 4 hours followed by filtration and washing with a mixture of DMF and methanol (1:1, 2 x 1 mL) 3 x 1 mL DMF and 2 x 1 mL dichloromethane to afford the desired product.

Step D: Resin bound 3-{4-[1-(4-Butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

200 μ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500 μ L dichloroethane was added to the above resin bound 3-{4-[(4-butoxyphenylamino)methyl]benzoylamino}propionic acid (50 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

Step E: 3-{4-[1-(4-Butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

The above resin bound 3-{4-[1-(4-butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid (50 mg) was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 μ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min

before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction pr. minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

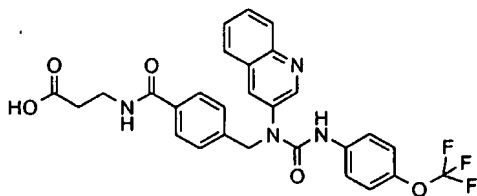
5

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.20 (s br, 1H); 8.50 (t, 1H); 8.09 (s, 1H); 7.73 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 7.10 (d, 2H); 6.90 (d, 2H); 4.90 (s, 2H); 3.95 (t, 2H); 3.45 (m, 2H); 2.50 (t, 2H); 1.60 (k, 2H) 1.42 (sx, 2H); 0.95 (t, 3H)

10 The following examples can be made as described above.

EXAMPLE 436 (general procedure (T))

3-{4-[1-Quinolin-3-yl-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

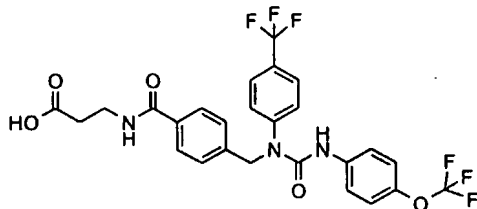


15

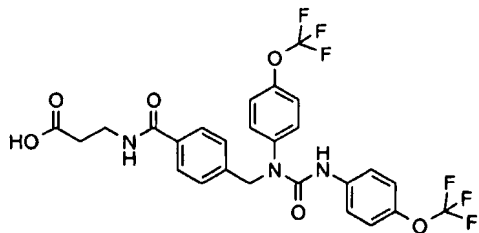
¹H NMR (400 MHz, DMSO-*d*₆): δ 12.20 (s br, 1H); 8.80 (m, 2H); 8.45 (t, 1H); 8.25 (s, 1H); 8.00 (d, 2H); 7.95 (d, 2H); 7.78 (m, 3H); 7.60 (t, 1H); 7.55 (d, 2H); 7.38 (d, 2H); 7.24 (d, 2H); 5.12 (s, 2H); 3.45 (m, 2H); 2.50 (t, 2H).

20 EXAMPLE 437 (general procedure (T))

3-{4-[3-(4-Trifluoromethoxyphenyl)-1-(4-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid



25 ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.15 (s br, 1H); 8.95 (s, 1H); 8.48 (t, 1H); 7.75 (d, 2H); 7.68 (d, 2H); 7.58 (d, 2H); 7.50 (d, 2H); 7.35 (d, 2H); 7.25 (d, 2H); 5.10 (s, 2H); 3.45 (m, 2H); 2.50 (t, 2H).

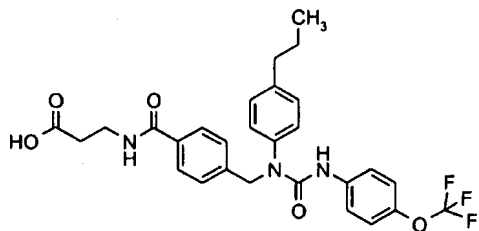
EXAMPLE 438 (general procedure (T))3-{4-[1,3-Bis(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

5

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.25 (s br, 1H); 8.65 (s, 1H); 8.48 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.35 (m, 6H); 7.22 (d, 2H); 5.00 (s, 2H); 3.40 (m, 2H); 2.50 (t, 2H).

EXAMPLE 439 (general procedure (T))

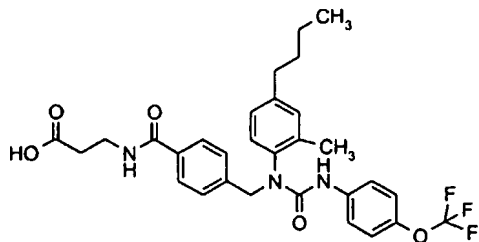
10 3-{4-[1-(4-Propylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



15 ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.20 (s, 1H); 8.45 (t, 1H); 8.30 (s, 1H); 7.73 (d, 2H); 7.52 (d, 2H); 7.32 (d, 2H); 7.20-7.10 (m, 6H); 4.95 (s, 2H); 3.45 (m, 2H); 2.50 (m, 4H); 1.60 (sx, 2H); 0.90 (t, 3H).

EXAMPLE 440 (general procedure (T))

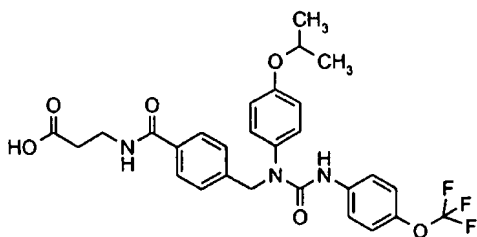
20 3-{4-[1-(4-Butyl-2-methylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.20 (s br, 1H); 8.45 (t, 1H); 7.87 (s, 1H); 7.75 (d, 2H); 7.52 (d, 2H); 7.30 (d, 2H); 7.22 (d, 2H); 7.10 (s, 1H) 7.05 (d, 1H); 6.95 (d, 1H); 5.15-4.85 (d br, 2H); 3.45 (m, 2H); 2.55-2.50 (m, 4H); 1.60 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

5 EXAMPLE 441 (general procedure (T))

3-{4-[1-(4-Isopropoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

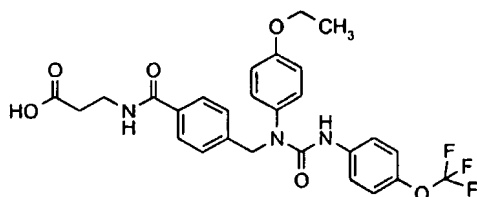


10 ^1H NMR ($\text{DMSO}-d_6$): δ 8.47 (t, 1H); 8.10 (s, 1H); 7.75 (d, 2H); 7.56 (d, 2H); 7.36 (d, 2H); 7.23 (d, 2H); 7.12 (d, 2H); 6.90 (d, 2H); 4.92 (s, 2H); 4.60 (q, 1H); 1.25 (d, 6H).

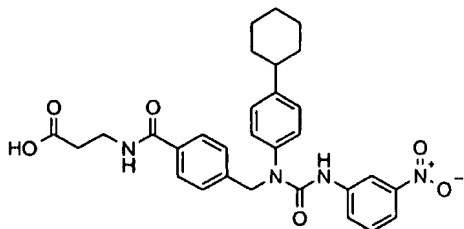
EXAMPLE 442 (general procedure (T))

3-{4-[1-(4-Ethoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

15 acid



^1H NMR ($\text{DMSO}-d_6$): δ 8.46 (t, 1H); 8.06 (s, 1H); 7.78 (d, 2H); 7.56 (d, 2H); 7.34 (d, 2H); 7.22 (d, 2H); 7.14 (d, 2H); 6.92 (d, 2H); 4.91 (s, 2H); 4.01 (q, 2H); 1.32 (t, 3H).

EXAMPLE 443 (general procedure (T))**3-{4-[1-(4-Cyclohexylphenyl)-3-(3-nitrophenyl)ureidomethyl]benzoylamino}propionic acid**

- 5 ^1H NMR (DMSO- d_6): δ 12.20 (s br, 1H); 8.78 (s, 1H); 8.45 (s+t, 2H); 7.92(d, 1H); 7.80 (d, 1H); 7.75 (d, 2H); 7.50 (t, 1H) 7.30 (d, 2H); 7.20 (d, 2H); 7.15 (d,2H); 4.95 (s, 2H); 3.45 (m, 2H); 2.50 (t, 2H); 1.90-1.10 (m, 11H)

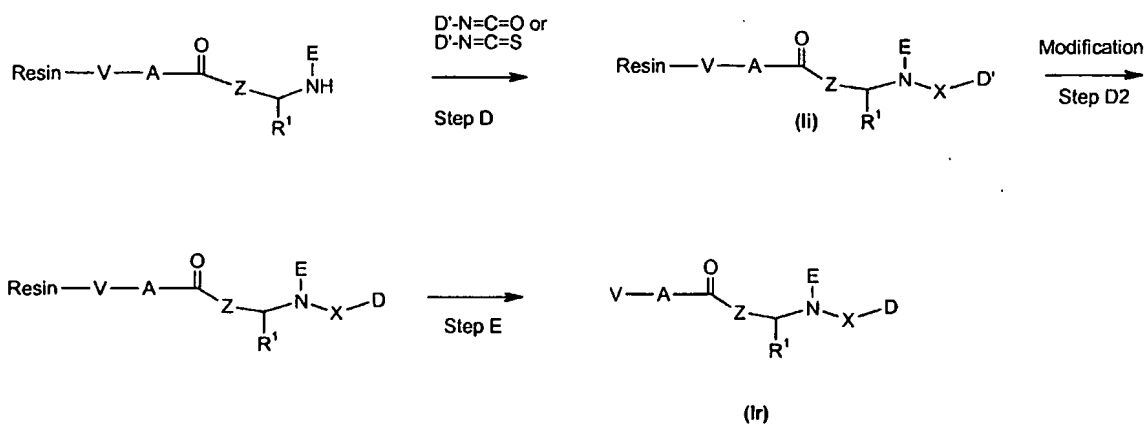
HPLC-MS (Method B): m/z = 545 ($M+1$). R_t = 7.47 min

10

General procedure (U) for the solid phase synthesis of compounds of the general formula (Ir):

Alternatively, molecules of general formula (Ii) obtained by the previously described general method (T) may be modified after step D. This applies to all general procedures comprising a

15 step similar to step D of procedure (T):



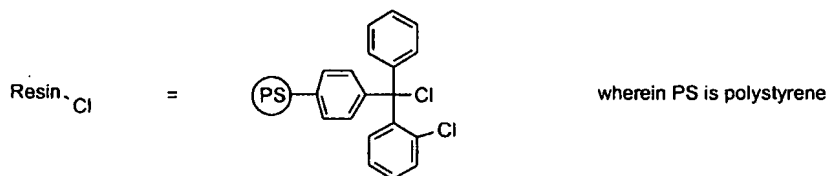
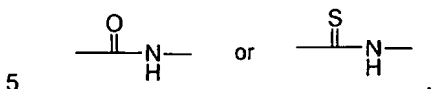
wherein

20

A, V, Z, R^1 , E and D are as defined for formula (I),

D' is a subgroup of D containing functionalities that may be further derivatized like sulfides, sulfoxides, or esters,

X is



Step D2: Oxidation of sulfides or sulfoxides

- 10 The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 132) and is performed by treating the resin bound intermediate with an oxidizing agent like 3-chloroperoxybenzoic acid or peracetic acid in a solvent like dichloromethane, 1,2-dichloroethane, THF or a mixture thereof. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with dichloro-
- 15 methane, 1,2-dichloroethane, DMF, *N*-methylpyrrolidinone, THF, DMSO or mixtures of two or more of these.

Step D2: Derivatization of esters

- Ester hydrolysis. The reaction is known (Hoekstra et al, Bioorg. Med. Chem. Lett. 1996, 6, 2371-2376) and is performed by treating the resin bound intermediate with a solution of potassium trimethylsilanolate in a solvent like THF or dioxan. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with dichloromethane, 1,2-dichloroethane, dioxan, DMF, *N*-methylpyrrolidinone, THF, DMSO or mixtures of two or more of these in combination with an acid like acetic acid
- 25 to afford the corresponding resin bound carboxylic acid.

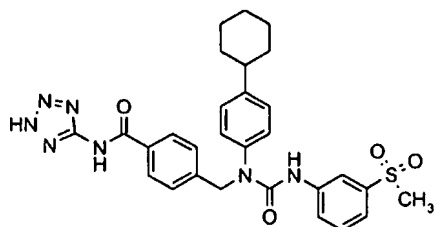
- The above resin bound carboxylic acid is converted into an active ester by the use of pentafluorophenyl trifluoroacetate or 4-nitrophenyl trifluoroacetate in the presence of pyridine in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these. The reaction is performed between
- 30

20°C and 40°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

The above resin bound active ester is allowed to react with nucleophiles like ammonia, primary or secondary amines, *N*-hydroxyamidines or hydrazides to afford resin bound carboxylic acid derivatives.

EXAMPLE 444 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



Step A: Resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide

150 µmol 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide was dissolved in a mixture of 250 µL dichloromethane, 250 µL DMF and 100 µL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with 2-chlorotrityl chloride. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane:-methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step C: Resin bound 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

The above resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide (50 mg) was treated with a 0.5 M solution of 4-cyclohexylaniline (0.25 mmol, 41.25 mg) in a mixture of DMF and trimethylorthoformate (1:1, 0.5 mL) and glacial acetic acid (50 µL) for 1 hour at 25°C followed sodium cyanoborohydride (250 µmol, 16 mg) dissolved in a mixture of DMF and methanol (1:1, 0.25 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of DMF and methanol (1:1, 2 x 1 mL), 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

Step D: Resin bound 4-[1-(4-cyclohexylphenyl)-3-(3-methylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

200 μ mol 3-Thiomethylphenylisocyanate dissolved in 500 μ L dichloroethane was added to the above resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

Step D2: Resin bound 4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

To the above resin bound 4-[1-(4-cyclohexylphenyl)-3-(3-methylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide was added a solution of 3-chloroperbenzoic acid (2.0-2.8 mmol) in 1,2-dichloroethane (500 μ L). The mixture was shaken overnight at 25 °C. Filtration followed by washing of the resin with dichloromethane (2 x 1 mL) afforded the resin bound title compound.

Step E: 4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

The above resin bound 4-[1-(4-cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg) was washed with DMF (4 x 1 mL), H₂O (2 x 1 mL), THF (3 x 1 mL) and dichloromethane (3 x 1 mL) and treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 μ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction pr. minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

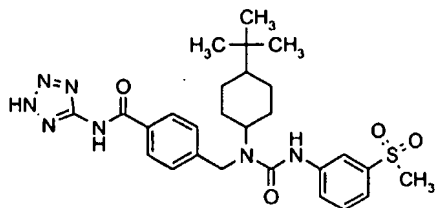
¹H NMR (300 MHz, DMSO-*d*₆): δ 12.30 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.75 (m, 1H); 7.52-7.42 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 3.15 (s, 3H); 1.85-1.60 (m, 5H); 1.50-1.15 (m, 6H).

HPLC-MS (method B) m/z = 574, R_t = 7.18 min.

The following examples can be made as described above.

5 EXAMPLE 445 (general procedure (U))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



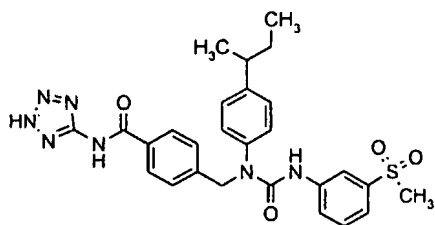
- 10 ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.30 (s br, 1H); 8.82 (s, 1H); 8.05 (d, 2H); 8.15-8.00 (m, 3H); 7.78 (d, 1H); 7.55-7.45 (m, 4H); 4.65 (s, 2H); 4.10 (t br, 1H); 3.13 (s, 3H); 1.83-0.90 (m, 9H); 0.85 (s, 9H).

HPLC-MS (method B) m/z = 554, R_t = 7.12 min.

15

EXAMPLE 446 (general procedure (U))

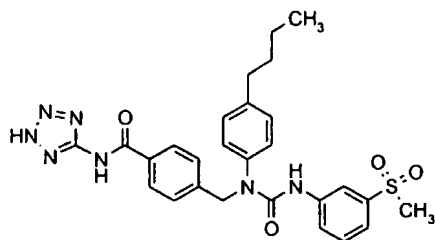
4-[1-(4-*sec*-Butylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



20

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.35 (s br, 1H); 8.65 (s, 1H); 8.10-8.00 (m, 4H); 7.75 (m, 1H); 7.52-7.42 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 3.15 (s, 3H); 2.55 (q, 1H); 1.55 (k, 2H); 1.20 (d, 3H); 0.75 (t, 3H).

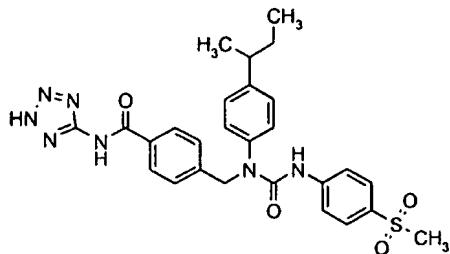
- 25 HPLC-MS (method B) m/z = 548, R_t = 6.03 min.

EXAMPLE 447 (general procedure (U))**4-[1-(4-Butylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

- 5 ^1H NMR ($\text{DMSO}-d_6$): δ 0.90 (3H, t), 1.42 (2H, sextet), 1.57 (2H, pentet), 2.58 (2H, partly hidden by DMSO), 3.15 (3H, s), 5.02 (2H, s), 7.21 (4H, s), 7.45-7.52 (4H, m), 7.85 (1H, m), 8.0-8.1 (3H, m), 8.61 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): R_t = 6.37 min, m/z = 548 ($M + 1$).

10

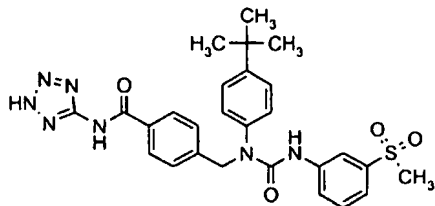
EXAMPLE 448 (general procedure (U))**4-[1-(4-sec-Butylphenyl)-3-(4-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide**

15

- ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.30 (s br, 1H); 8.72 (s, 1H); 8.05 (d, 2H); 7.75 (d, 2H); 7.70 (d, 2H); 7.45 (d, 2H); 7.20 (s, 4H); 5.00 (s, 2H); 3.11 (s, 3H); 2.60 (q, 1H); 1.55 (k, 2H); 1.20 (d, 3H); 0.75 (t, 3H).

- 20 HPLC-MS (method B) m/z = 548, R_t = 6.03 min.

365

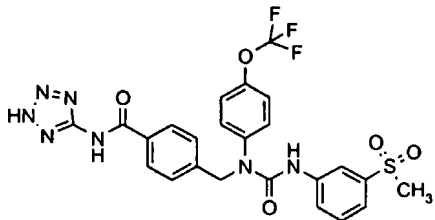
EXAMPLE 449 (general procedure (U))4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

5

¹H NMR (DMSO-*d*₆): δ 1.30 (9H, s), 3.18 (3H, s), 5.03 (2H, s), 7.24 (2H, d), 7.41 (2H, d), 7.45-7.55 (8H, m), 7.85 (1H, m), 8.05 (2H, d), 8.08 (1H, s), 8.70 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): R_t = 5.97 min, m/z = 548 (M + 1).

10

EXAMPLE 450 (general procedure (U))4-[3-(3-Methylsulfonylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

15

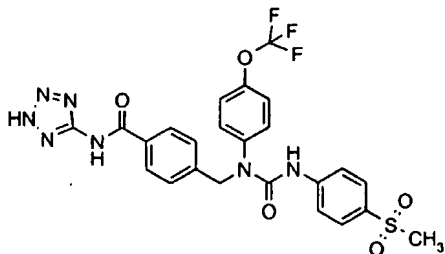
¹H NMR (300 MHz, DMSO-*d*₆): δ 12.35 (s, 1H); 8.85 (s, 1H); 8.05 (d, 2H); 7.75 (m, 1H); 7.55-7.35 (m, 9H); 7.20 (s, 4H); 5.05 (s, 2H); 3.15 (s, 3H).

HPLC-MS (method B) m/z = 576, R_t = 5.42 min.

20

EXAMPLE 451 (general procedure (U))

4-[3-(4-Methylsulfonylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

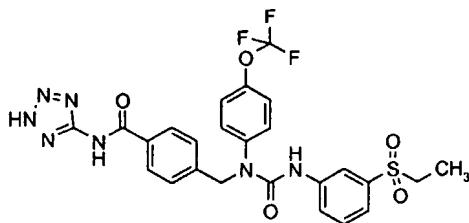
^1H NMR (300 MHz, DMSO- d_6): δ 12.35 (s, 1H); 8.95 (s, 1H); 8.05 (d, 2H); 7.70 (d, 2H); 7.65 (d, 2H); 7.49 (d, 2H); 7.43 (d, 2H); 7.45 (d, 2H); 5.05 (s, 2H); 3.12 (s, 3H).

HPLC-MS (method B) m/z = 576, R_t = 5.42 min.

10

EXAMPLE 452 (general procedure (U))

4-[3-(3-Ethylsulfonylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

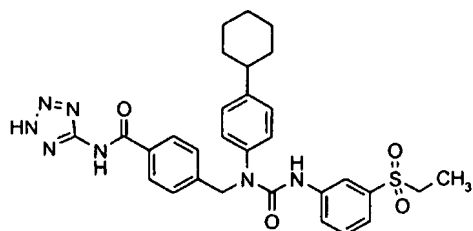


15

HPLC-MS (method B) m/z = 590, R_t = 5.90 min.

EXAMPLE 453 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-ethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



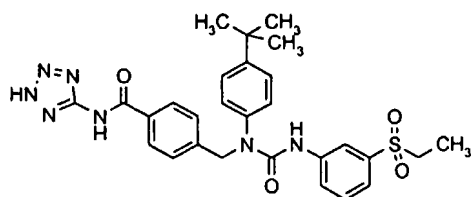
5

HPLC-MS (method B) m/z = 588, R_t = 7.10 min.

EXAMPLE 454 (general procedure (U))

4-[1-(4-*tert*-Butylphenyl)-3-(3-ethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

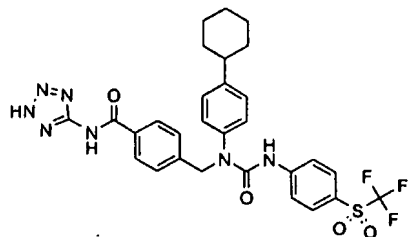
10



HPLC-MS (method B) m/z = 561, R_t = 6.40 min.

EXAMPLE 455 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

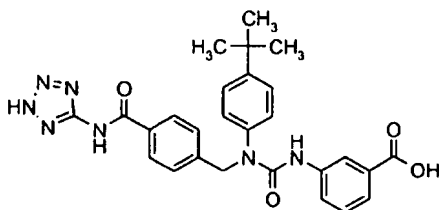


20 ^1H NMR (DMSO- d_6): δ 9.20 (1H, broad), 7.90 (5H, m), 7.79 (1H, dd), 7.44 (2H, d), 7.21 (4H, s), 5.00 (2H, broad), 1.90-1.00 (10H, m).

HPLC-MS (method B): m/z: 628, R_t = 8.05 min.

EXAMPLE 456 (general procedure (U))

3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid



5

Step A: Resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide

1500 μ mol 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide was dissolved in a mixture of 2500 μ L dichloromethane, 2500 μ L DMF and 1000 μ L diisopropylethylamine and added to 500 mg
 10 polystyrene resin functionalized with 2-chlorotriyl chloride. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 10 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 10 mL DMF.

Step C: Resin bound 4-[(4-*tert*-butylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

15 The above resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide (500 mg) was treated with a 0.5 M solution of 4-*tert*-butylaniline (2.5 mmol, 412.5 mg) in a mixture of DMF and trimethyl-orthoformate (1:1, 5 mL) and glacial acetic acid (500 μ L) for 1 hour at 25°C followed by sodium cyanoborohydride (2.5 mmol, 160 mg) dissolved in a mixture of DMF and methanol (1:1, 2.5 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of
 20 methanol and DMF (1:1, 2 x 10 mL), DMF (3 x 10 mL) and dichloromethane (2 x 10 mL) afforded the desired product.

Step D: Resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}-benzoic acid methyl ester

25 2.50 mmol 3-isocyanatobenzoic acid methyl ester dissolved in 5 mL dichloroethane was added to the above resin 4-[(4-*tert*-butylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (500 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing of the resin with dichloromethane (2 x 10 mL), DMF (2 x 10 mL) and THF (3 x 10 mL) afforded the resin bound title compound.

30

Step D2: Derivatization of estersResin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid

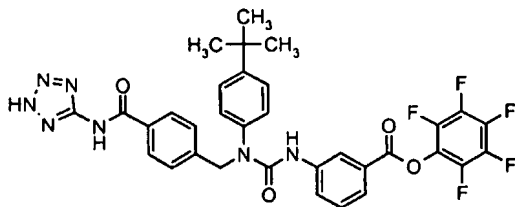
To the above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid methyl ester was added a solution of potassium trimethylsilanolate in THF (1M, 5 mL). The mixture was shaken 4 hours at 25°C, filtered and allowed to react with a solution of acetic acid in THF (20%, 5 mL) at 25°C overnight. Filtration followed by washing of the resin with dichloromethane (2 x 10 mL) afforded the resin bound title compound.

Step E: 3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid

The above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid (500 mg) was washed with DMF (4 x 10 mL), H₂O (2 x 10 mL), THF (3 x 10 mL), dichloromethane (3 x 10 mL) and treated with 10 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 10 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was recrystallised in acetonitrile to afford the title compound.

¹H NMR (200 MHz, DMSO-*d*₆): δ 12.90 (s br, 1H); 12.35 (s br, 1H); 8.50 (s, 1H); 8.05 (d, 2H); 7.75 (d, 1H) 7.60-7.15 (m, 8H); 5.00 (s, 2H); 1.22 (s, 9H).

HPLC-MS (method B) *m/z* = 514, *R*_t = 5.98 min.

EXAMPLE 457 (general procedure (U))3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester

Step D2: Derivatisation of estersResin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester

To the above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-ureido}benzoic acid was added a solution of pyridine (500 μ L) in DMF (5 mL) followed by pentafluorophenyl trifluoroacetate (850 μ L). The mixture was shaken for 4 hours at 25 °C, filtered and washed with DMF (2 x 10 mL), affording the resin bound title compound.

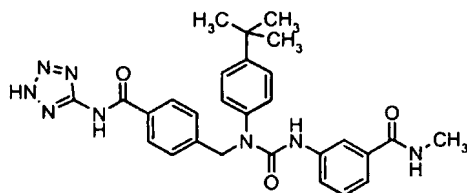
10 Step E: 3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester

The above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-ureido}benzoic acid pentafluorophenyl ester (500 mg) was washed with DMF (4 x 10 mL), H₂O (2 x 10 mL), THF (3 x 10 mL), dichloromethane (3 x 10 mL) and treated with 10 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 10 mL dichloromethane. The combined extracts were concentrated in vacuo.
15 The residue was recrystallised in CH₃CN to afford the title compound.

¹H NMR (300 MHz, DMSO-*d*₆): δ 12.30 (s br, 1H); 8.05 (d, 2H); 8.00-7.60 (m, 2H) 7.55-7.15 (m, 8H); 5.00 (s, 2H); 1.22 (s, 9H).

20

HPLC-MS (method B) *m/z* = 680, *R*_t = 8.27 min.

EXAMPLE 458 (general procedure (U))*N*-Methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzamide

25

Step D2: Derivatisation of estersResin bound *N*-methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-ureido}benzamide

30 To the above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-ureido}benzoic acid pentafluorophenyl ester was added a solution of methylamine in THF

(2M, 5 mL). The mixture was shaken at 25 °C overnight, filtered and washed with THF (2 x 10 mL), affording the resin bound title compound.

Step E: N-Methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}-benzamide

The above resin bound *N*-methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]ureido}benzamide (500 mg) was washed with DMF (4 x 10 mL), H₂O (2 x 10 mL), THF (3 x 10 mL), dichloromethane (3 x 10 mL) and treated with 10 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 10 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was recrystallized from CH₃CN to afford the title compound.

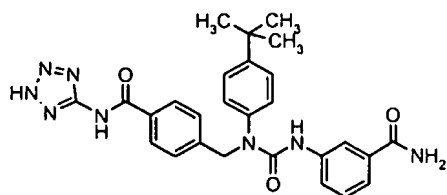
¹H NMR (200 MHz, DMSO-*d*₆): δ 12.35 (s br, 1H); 8.40 (s, 1H); 8.43 (q, 1H); 8.05 (d, 2H); 7.85 (s, 1H); 7.63 (d, 1H); 7.50-7.15 (m, 8H); 5.03 (s, 2H); 2.80 (d, 3H); 1.25 (s, 9H).

HPLC-MS (method B): *m/z* = 527, *R*_t = 5.55 min

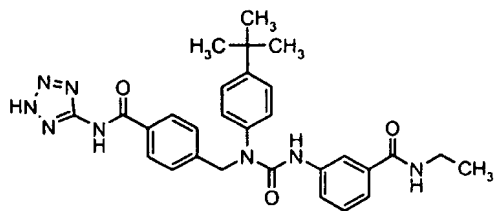
The following examples were made as described above.

EXAMPLE 459 (general procedure (U))

3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzamide



HPLC-MS (method B): *m/z* = 513, *R*_t = 5.52 min.

EXAMPLE 460 (general procedure (U))N-Ethyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzamide

- 5 ^1H NMR (200 MHz, $\text{DMSO-}d_6$): δ 12.35 (s br, 1H); 8.40 (m, 2H); 8.05 (d, 2H); 7.80 (s, 1H); 7.63 (d, 1H); 7.55-7.15 (m, 8H); 5.03 (s, 2H); 3.30 (dq, 2H); 1.30 (s, 9H); 1.12 (t, 3H).

HPLC-MS (method B): m/z = 541, R_t = 5.83 min.

2,33 (m, 4H) ; 1,71 (d, J = 10Hz, 2H); 1,62 (qd, J = 4 et 12Hz, 2H) ; 1,3 (m, 2H).
SM/CL : m/z = 652,4 (M+H).

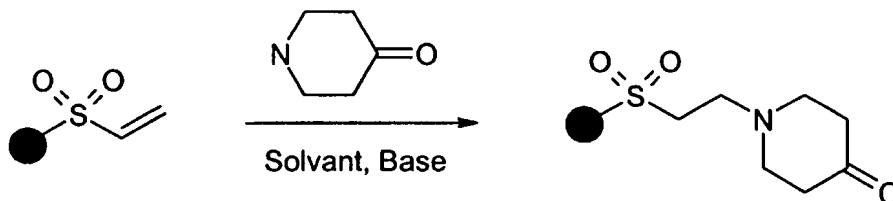
Une série de sulfonamides a été synthétisée selon cette procédure. Les groupes R₁, X₁, X₂ et X₃ que l'on peut envisager, sont ceux illustrés aux points (A et B3a), A, (A et B3c) et B3b respectivement.

D) Synthèse de pipéridines tri-substituées en phase solide

Elle s'effectue à partir de la résine vinyle sulfone (Kroll, F.E.K. ; Morphy, R. ; Rees, D. ; Gani, D. *Tetrahedron Lett.* 1997, 38, 8573-8576 ; Brown, A.R. *J. Comb. Chem.* 1999, 1, 283-285) selon le schéma suivant :

10 D1) Préparation de la résine

Elle s'effectue selon le schéma suivant :



Au chlorhydrate hydraté de pipéridone dilué dans la diméthylformamide est ajoutée de la triéthylamine (1 éq.). Le mélange est chauffé jusqu'à dissolution complète de la cétone. Cette solution est ajoutée à la résine vinyle sulfone (0,05 éq.) prégonflée dans la diméthylformamide. Après 24 à 72 heures d'agitation à température ambiante, la résine est filtrée puis lavée plusieurs fois avec de la diméthylformamide, du tétrahydrofurane, du diéther et du dichlorométhane.

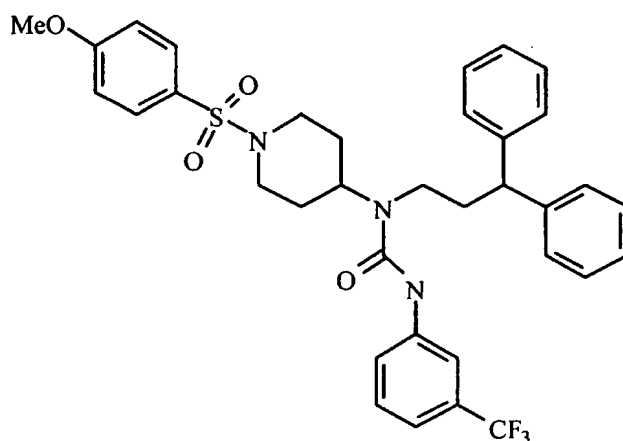
Préparation 4

1,5 g de la résine vinyle sulfone (Novabiochem, taux de charge de 1 mmol/g, 1,5 mmol) est prégonflée dans 50 ml de diméthylformamide. Dans le même temps, 2,3 g (15 mmol, 10 éq.) de chlorhydrate hydraté de pipéridone et 1,8 g (15 mmol, 10 éq.) de triéthylamine sont chauffés dans 100 ml de diméthylformamide jusqu'à dissolution complète. La solution jaunâtre est versée chaude sur la résine et le mélange agité 24 heures à température ambiante. La résine est filtrée puis lavée avec de la diméthylformamide, du tétrahydrofurane, du diéther et du dichlorométhane (3 fois chaque solvant) puis séchée sous vide. 1,7 g de résine jaune pâle sont isolés avec un taux de charge de 1 mmol/g calculé d'après l'analyse élémentaire de l'azote.

- 62 -

diméthylformamide ou le tétrahydrofurane. Le chlorure de sulfonyl (1,1 à 2 éq.) dissout dans des solvants anhydres tels que le dichlorométhane, le diméthylformamide ou le tétrahydrofurane est ajouté, suivi de la pipéridine 4-aminodisubstituée. Le mélange est agité de 16 à 48 heures. La résine aminométhyle (0,1 à 1,5 éq.) est ajoutée et la réaction agitée toute la nuit. Dans certains cas, de la résine échangeuse d'ions telle que IRA68 ou SAX est ajoutée et le mélange agité à température ambiante de 1 à 18 heures. Les résines sont filtrées sur fritté, sur cartouche de résine échangeuse d'ions SAX (500 mg, Interchim) ou sur cartouche d'alumine basique (500 mg, Interchim).

- 10 Exemple C3 : Urée de N-(3,3-diphénylpropyl)-N-{1-[(4-méthoxyphényl)sulfonyl]-4-pipéridinyl}-N'-[3-(trifluorométhyl)phényl] ($C_{35}H_{36}F_3N_3O_4S$, $M = 651,75$)



27,5 mg (100 μ mol, 2 éq.) de résine morpholinométhyle est prégonflée dans du tétrahydrofurane anhydre, on ajoute alors le chlorure de 4-méthoxyphénylsulfonyl (15,5 mg, 0,075 mmol, 1,5 éq.) puis l'urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluorométhyl)phényl] (24,3 mg, 0,05 mmol). Le mélange est agité toute la nuit. Les résines aminométhyle (20 mg) et échangeuse d'ions SAX sont ajoutées et le mélange est agité toute la nuit. Les résines sont filtrées et rincées au dichlorométhane. L'huile obtenue après évaporation est passée sur une cartouche de gel de silice (500 mg, Interchim) en éluant avec de l'acétate d'éthyle pour obtenir après concentration 18 mg (rdt = 56 %) d'un solide blanc.

RMN 1H (CD_3OD , 400 MHz) δ : 7,71 (d, $J = 9,2Hz$, 2H) ; 7,65 (s, 1H) ; 7,51 (d, 1H) ; 7,41 (t, $J = 7,6Hz$, 1H) ; 7,29 (m, 9H) ; 7,20 (m, 2H) ; 7,11 (dd, $J = 1,6$ et 6,8Hz, 2H) ; 3,88 (s, 3H, OCH_3) ; 3,77 (d, $J = 12,4Hz$, 2H) ; 3,16 (t, $J = 8Hz$, 2H) ;

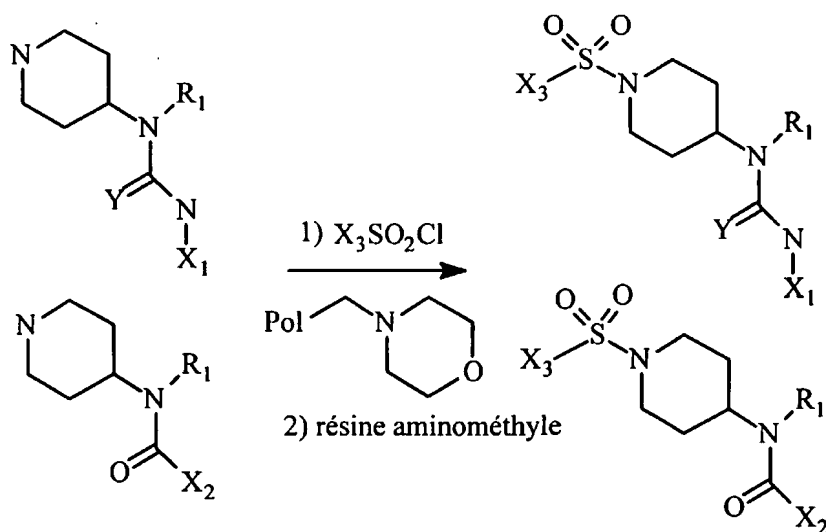
117 mg (175 μ mol, 3,5 eq.) de résine P-EDC est prégonflée dans 1,5 ml de dichlorométhane anhydre. L'acide acétique (7,5 mg, 125 μ mol, 2,5 eq.) est ajouté et le mélange agité 10 minutes. Puis l'urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluorométhyl)phényl] (24,3 mg, 50 μ mol) est ajoutée à son
 5 tour et le mélange agité toute la nuit. La résine est filtrée et le filtrat concentré. L'huile obtenue est passée sur une cartouche de gel de silice en éluant avec un mélange équimolaire d'heptane et d'acétate d'éthyle pour obtenir après concentration 16 mg (rdt = 62 %) d'une mousse blanche.

RMN ^1H (CD_3OD , 400 MHz) δ : 7,71 (s, 1H) ; 7,58 (d, J = 8,4Hz, 1H) ; 7,43 (t, J = 8Hz, 1H) ; 7,28 (m, 9H) ; 7,17 (m, 2H) ; 4,56 (dd, J = 2 et 11,2Hz, 1H) ; 4,17 (m, 1H) ; 3,96 (t, J = 7,6Hz, 1H) ; 3,88 (d, J = 12Hz, 1H) ; 3,19 (q, J = 4 et 8Hz, 2H) ; 3,1 (t, J = 12Hz, 1H) ; 2,58 (t, J = 12Hz, 1H) ; 2,37 (m, 2H) ; 2,06 (s, 3H, CH_3) ; 1,72 (t, J = 14,4Hz, 2H) ; 1,43 (qd, J = 4 et 12,4Hz, 2H).
 SM/CL : m/z = 524,3 (M+H).

15 Une série d'amides a été synthétisée selon cette procédure. Les groupes R_1 , X_1 et X_2 que l'on peut envisager, sont ceux illustrés aux points (A et B3a), A, (A et B3c) respectivement.

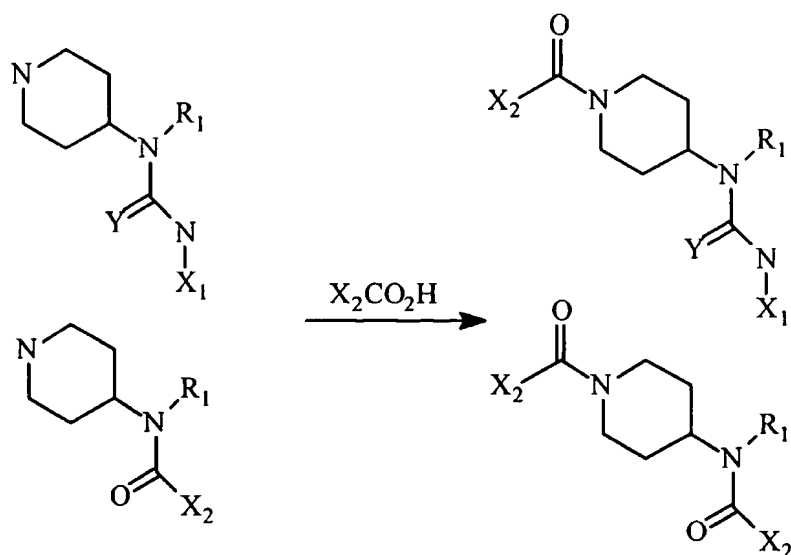
C3) Fonctionnalisation avec des chlorures de sulfonyles

Elle s'effectue selon le schéma suivant :



Procédure générale : la résine morpholinométhyle (Novabiochem, 2 à 3 eq.) est prégonflée dans des solvants anhydres tels que le dichlorométhane, le

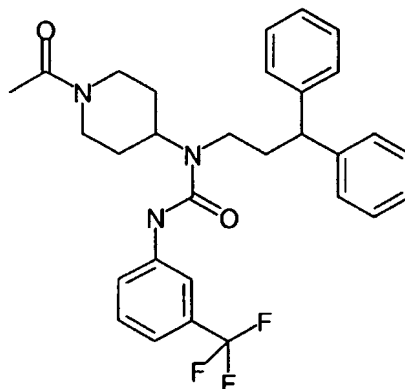
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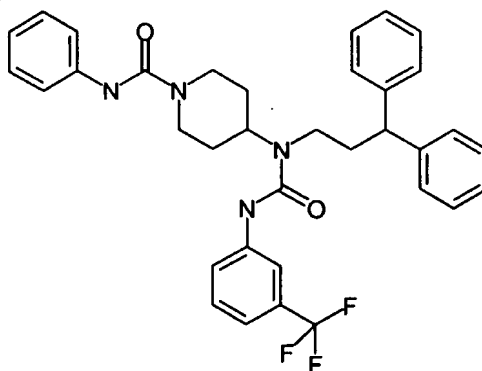
Procédure générale : la résine P-EDC (1,3 à 3 éq.) est prégonflée dans du dichlorométhane anhydre. L'acide carboxylique (1,1 à 2,5 éq.) est dissout dans un solvant anhydre tel que le dichlorométhane, la diméthylformamide ou le tétrahydrofurane et ajouté à la résine. Ce mélange est agité de 5 à 30 minutes à température ambiante. On ajoute alors à ce mélange la pipéridine 4-aminodisubstituée, sous forme de base libre, en solution dans un solvant anhydre tel que le dichlorométhane, le diméthylformamide ou le tétrahydrofurane et on agite le tout à température ambiante de 1 à 18 heures. Dans certains cas, de la résine échangeuse d'ions telle que IRA68 ou SAX est ajoutée et le mélange agité à nouveau à température ambiante de 1 à 18 heures. Les résines sont filtrées sur fritté, sur cartouche de résine échangeuse d'ions SAX (500 mg, Interchim) ou sur cartouche d'alumine basique (500 mg, Interchim).

Exemple C2 : Urée de N-(1-acétyl-4-pipéridinyl)-N-(3,3-diphénylpropyl)-

N'-[3-(trifluorométhyl) phényl] ($C_{30}H_{32}F_3N_3O_2$, $M = 523,60$)



Exemple C1 : Carboxamide de 4-((3,3-diphénylpropyl){[3-(trifluorométhyl)anilino] carbonyl} amino)-N-phényl-1-pipéridine ($C_{35}H_{35}F_3N_4O_2$, M = 600,68)



- 5 L'urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluorométhyl)phényl] (24 mg, 0,05 mmol) est dissoute dans du dichlorométhane. Le phénylisocyanate (9 mg, 0,075 mmol, 1,5 éq.) est ajouté et le mélange agité pendant 2,5 heures. La résine aminométhyle (0,02 mmol) est ajoutée et la réaction à nouveau agitée toute la nuit. La résine est filtrée, rincée avec du dichlorométhane et le filtrat concentré.
- 10 L'huile obtenue est passée sur une cartouche de gel de silice en éluant avec un mélange équimolaire d'heptane et d'acétate d'éthyle pour obtenir après concentration 12 mg (rdt = 40 %) d'une huile jaune.

RMN 1H (CD_3OD , 400 MHz) δ : 7,72 (s, 1H) ; 7,58 (d, 1H) ; 7,44 (m, 1H) ; 7,38 (m, 2H) ; 7,29 (m, 12H) ; 7,12 (m, 2H) ; 7,07 (m, 1H) ; 4,2 (d, J = 12,4Hz, 3H) ; 3,21 (t, J = 8Hz, 2H) ; 2,9 (t, J = 12,4Hz, 2H) ; 2,38 (q, J = 8Hz, 2H) ; 1,73 (d, J = 10Hz, 2H) ; 1,54 (qd, J = 3,6 et 12Hz, 2H). SM/CL : m/z = 601,4 (M+H).

15

Une série d'urées (Y = O) et de thiourées (Y = S) ont été synthétisées selon cette procédure. Les groupes R_1 , X_1 et X_2 que l'on peut envisager, sont ceux illustrés aux points ci-dessus (A et B3a), A, et (A et B3c) respectivement.

20 C2) Fonctionnalisation avec des acides carboxyliques

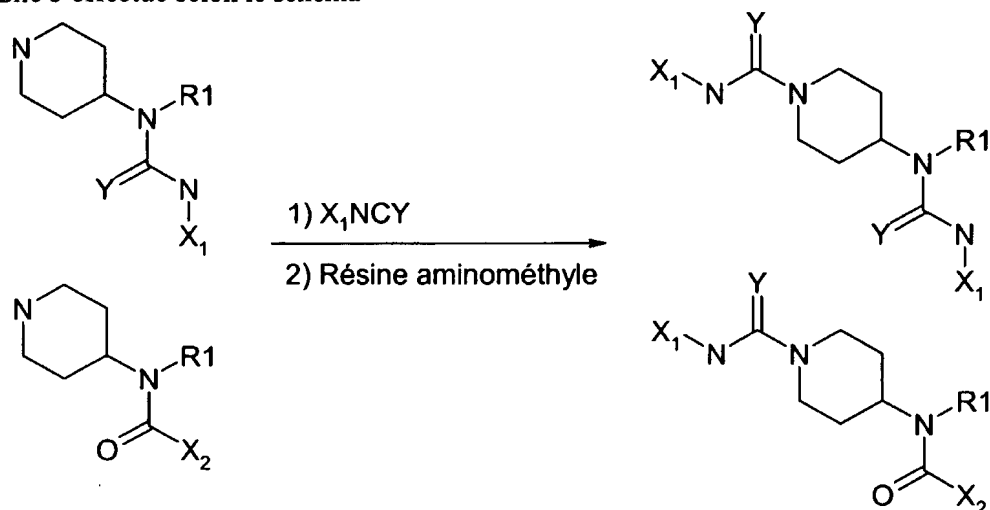
Elle s'effectue selon le schéma suivant

Une série d'amides a été synthétisée selon cette procédure. Les groupes R_1 envisagés sont ceux illustrés aux points A et B3a ci-dessus. Les groupes X_2 sont illustrés au point A ci-dessus.

C) Fonctionnalisation de la partie pipéridine en solution

5 C1) Obtention de pipéridine avec $R_3 = -C(Y)NHX_1$

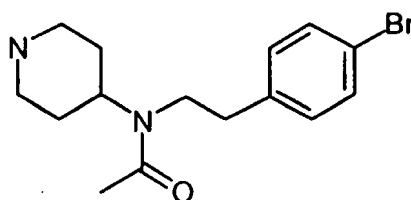
Elle s'effectue selon le schéma



- Procédure générale : à la pipéridine sous forme de base libre diluée dans du dichlorométhane, est ajouté un isocyanate ou isothiocyanate (1,1 à 1,5 éq.). Le mélange est agité d'une à 18 heures à température ambiante. La résine aminométhyle (0,2 à 1 éq.) est ajoutée et le mélange à nouveau agité de 2 à 18 heures. Dans certains cas, de la résine échangeuse d'ions telle que IRA68 ou SAX est ajoutée. Les résines sont filtrées et le filtrat concentré. Dans certains cas, le produit est dissout dans du dichlorométhane ou de l'acétate d'éthyle puis filtré sur une catouche de gel de silice ou d'alumine basique (500 mg, Interchim).

Procédure générale : la résine "amine secondaire" est prégonflée dans des solvants comme le dichlorométhane, le diméthylformamide ou le tétrahydrofurane. Puis l'acide carboxylique (3 à 5 éq.), l'hexafluorophosphate de benzo-triazol-1-yl-oxy-*tris*-pyrrolidino phosphonium (PyBoP, 3 à 5 éq.) et la diisopropyléthylamine (6 à 10 éq.) sont ajoutés et le mélange agité 24 heures à température ambiante. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, le diméthylformamide et le tétrahydrofurane, puis séchée sous vide. On agite ensuite la résine de 1 à 4 heures en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

Exemple B3d : Acétamide de N-[2-(4-bromophényl)éthyl]-N-(4-pipéridinyl)
(C₁₅H₂₁BrN₂O, M = 325,25)



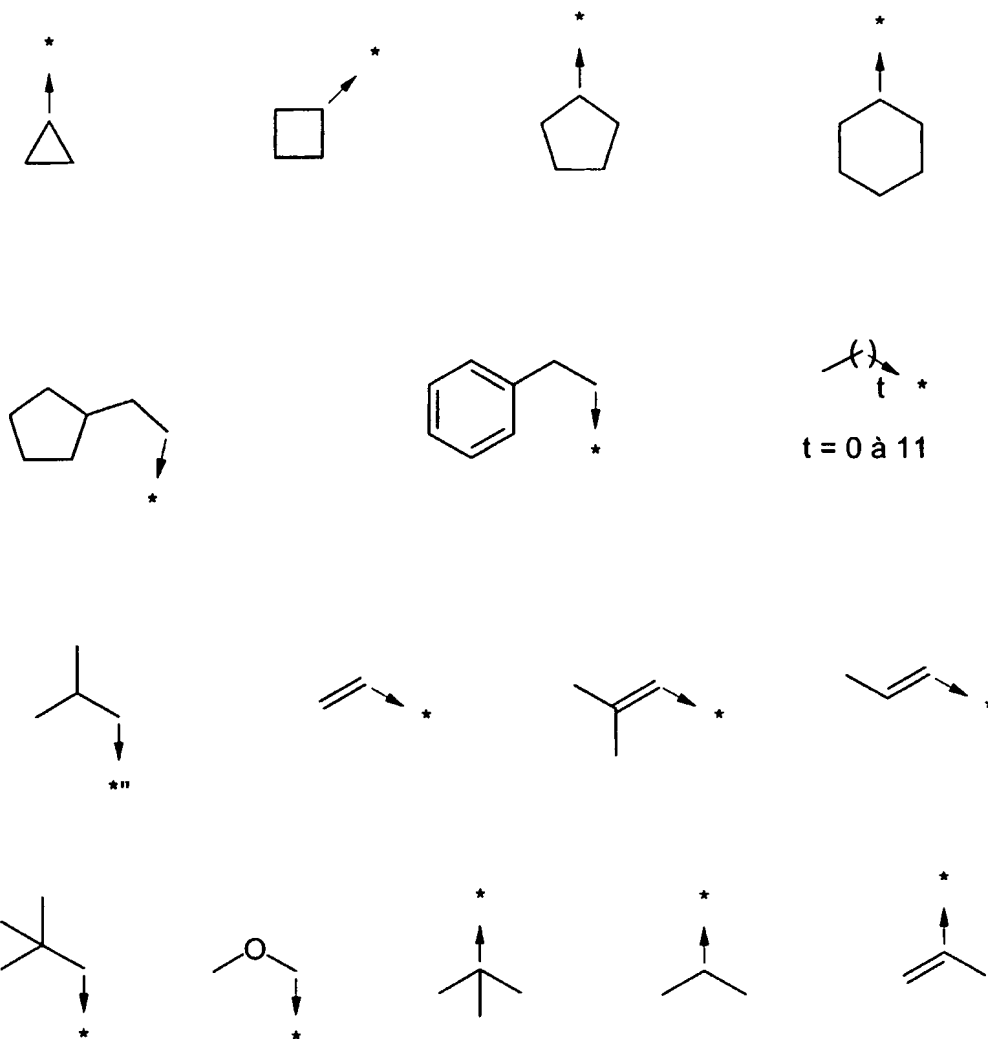
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55 mg (50 µmol) de la résine (voir préparation 3) sont prégonflés dans de la diméthylformamide anhydre. On ajoute ensuite l'acide acétique (8,8 mg, 150 µmol, 3 éq.), le PyBoP (76 mg, 150 µmol, 3 éq.) puis la diisopropyléthylamine (38 mg, 300 µmol, 6 éq.) et le tout est agité toute la nuit. La résine est filtrée, rincée au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On ajoute 800 µl d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et on agite 1,5 heure à température ambiante. La résine est filtrée et rincée au dichlorométhane. Le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium pour obtenir 11 mg d'une huile brune (rdt = 68 %).

25

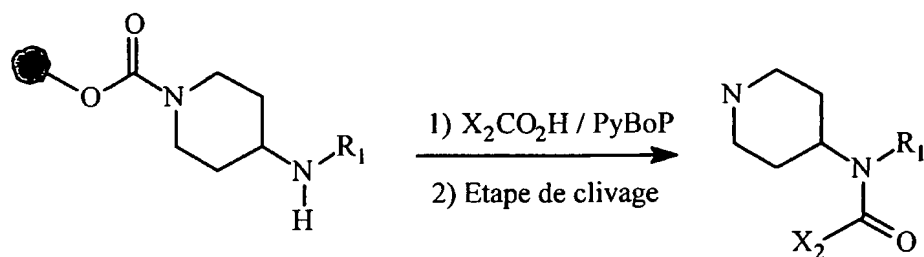
RMN ¹H (CD₃OD, 400 MHz) δ : 7,44 (m, 2H); 7,20 (m, 2H); 4,05 (m, 1H); 3,45 (m, 2H); 3,10 (m, 2H); 2,83 (m, 2H); 2,64 (m, 2H); 2,13 (s, 3H) ; 1,73 (m, 4H). SM/CL : m/z = 325,2 (M+H).

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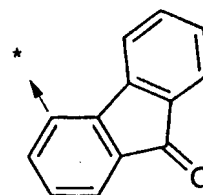
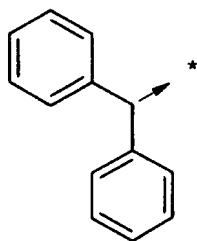
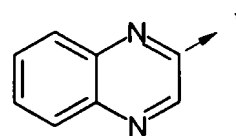
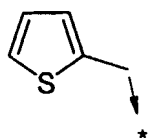
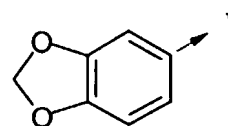
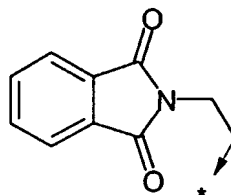
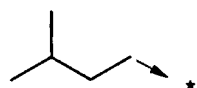
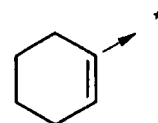
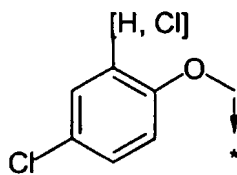
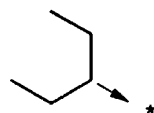
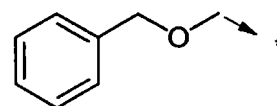
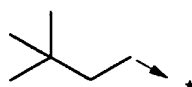
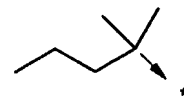
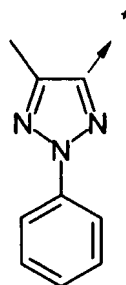
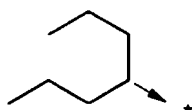
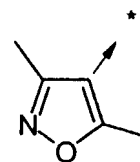
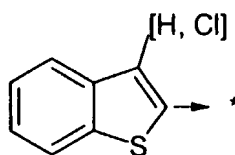
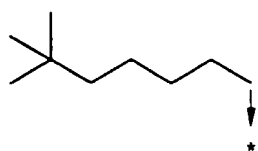


B3d) Fonctionnalisation avec des acides carboxyliques

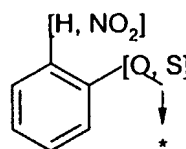
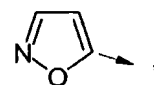
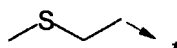
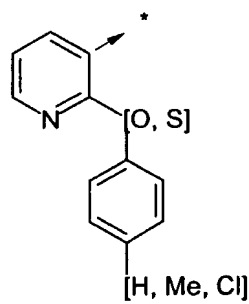
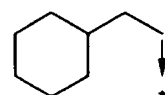
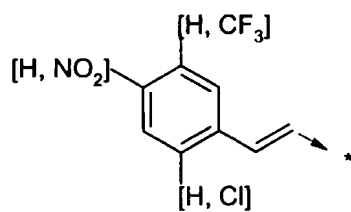
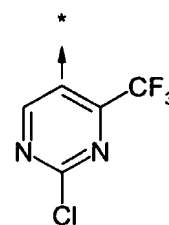
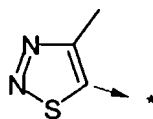
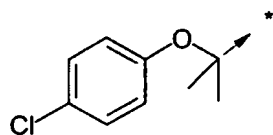
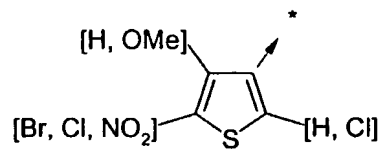
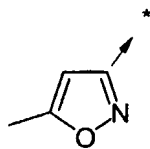
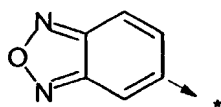
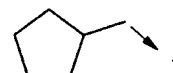
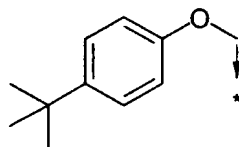
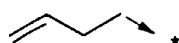
Elle s'effectue selon la procédure décrite dans la littérature (Kobayashi, S ; Aoki, Y., *J. Comb. Chem.* **1999**, *1*, 371-372) suivant le schéma suivant :



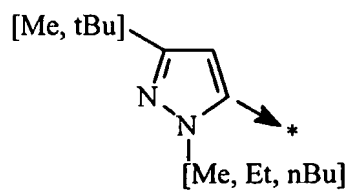
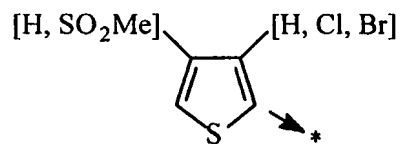
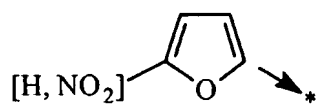
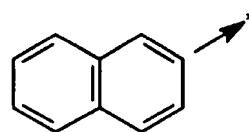
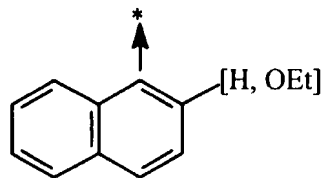
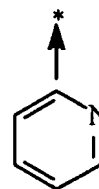
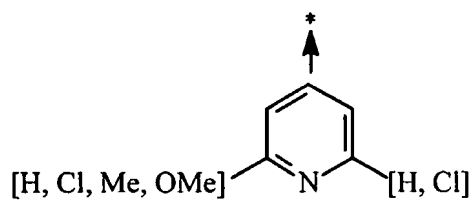
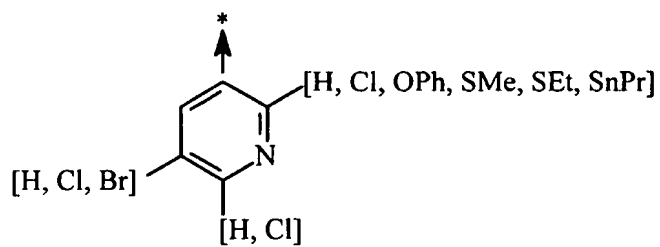
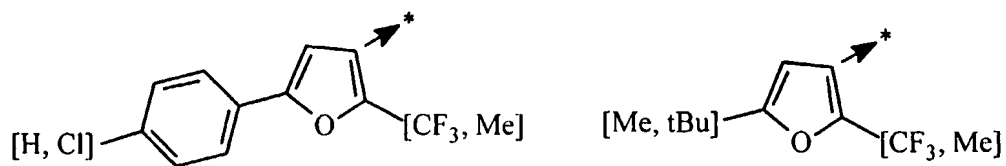
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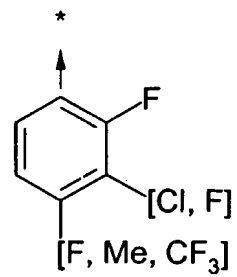
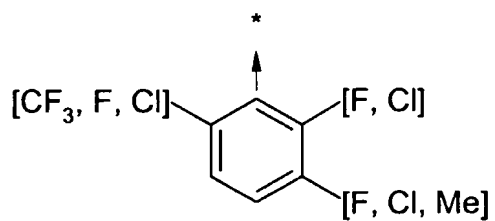
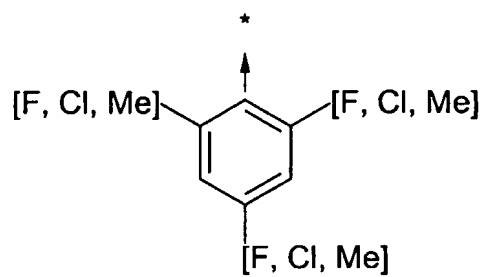
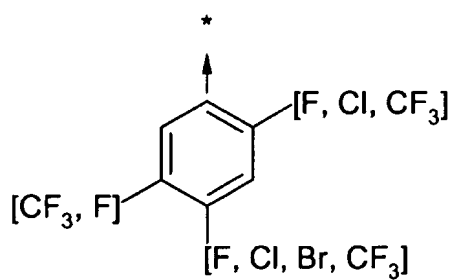
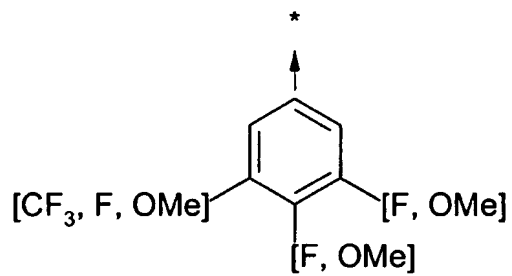
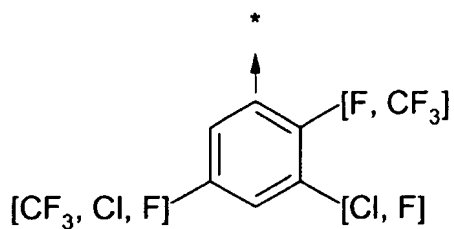
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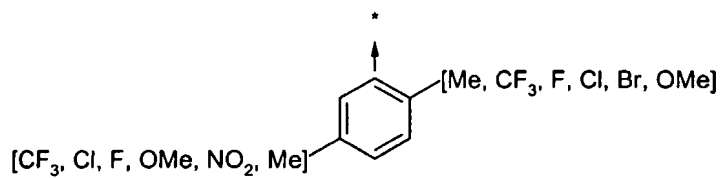
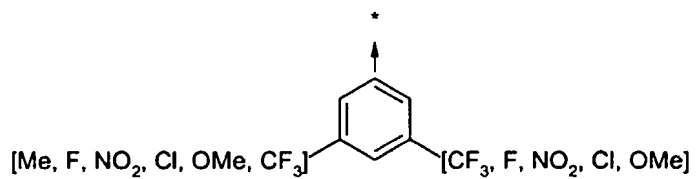
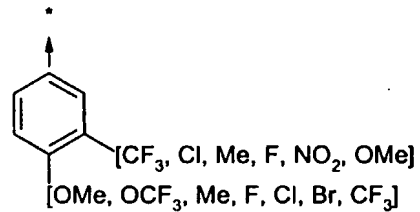
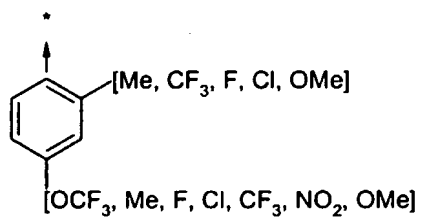
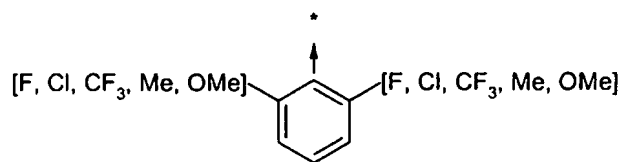
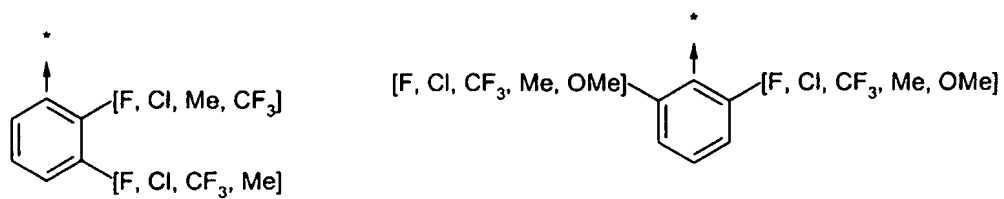
- 53 -



- 52 -



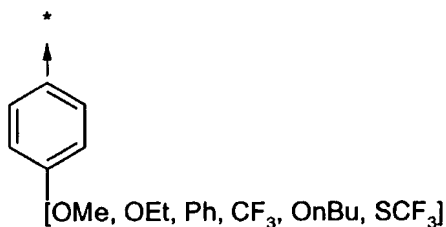
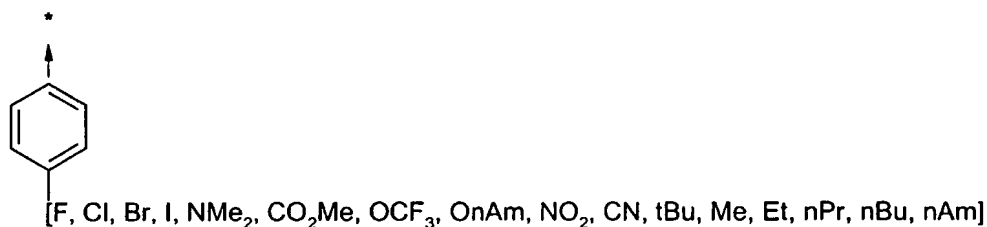
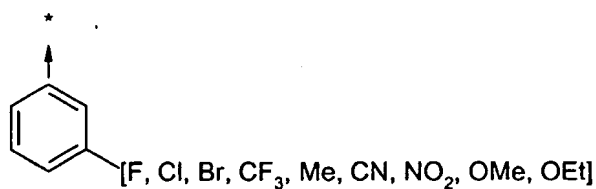
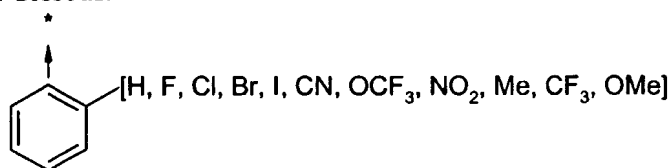
- 51 -



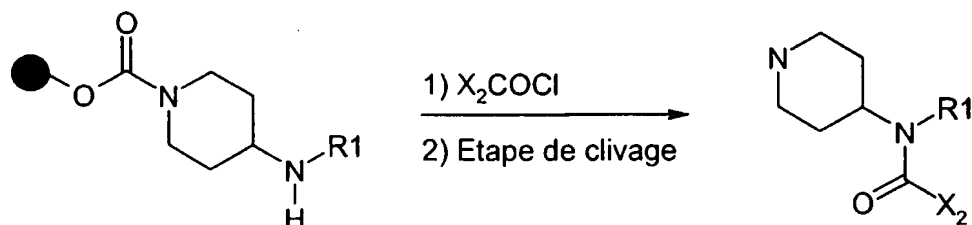
- 50 -

RMN ^1H (CD_3OD , 400 MHz) δ : 7,64 (dd, $J = 0,8$ et $4,8\text{Hz}$, 1H); 7,44 (d, $J = 8,4\text{Hz}$, 2H); 7,36 (d, $J = 3,6\text{Hz}$, 1H); 7,14 (m, 3H); 4,11 (m, 1H); 3,61 (t, $J = 8\text{Hz}$, 2H); 3,09 (d, $J = 12\text{Hz}$, 2H); 2,92 (m, 2H); 2,54 (m, 2H); 1,82 (m, 2H); 1,7 (m, 2H).
SM/CL : $m/z = 393,1$ (M+H).

- 5 Une série d'amides a été synthétisée selon cette procédure. Les groupes R_1 envisagés sont ceux illustrés aux points A et B3a ci-dessus. Les groupes X_2 sont illustrés ci-dessous.

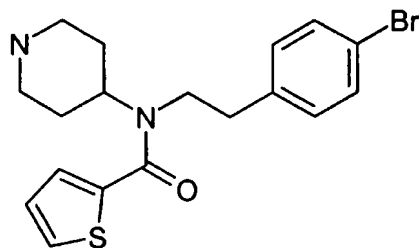


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Procédure générale : la résine "amine secondaire" est prégonflée dans des solvants comme le dichlorométhane, le diméthylformamide ou le tétrahydrofurane. Puis le chlorure d'acide (5 à 10 éq.) et la triéthylamine (6 à 12 éq.) sont ajoutés et le mélange agité de 12 à 24 heures à température ambiante. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, le diméthylformamide et le tétrahydrofurane, puis séchée sous vide. On agite ensuite la résine de 1 à 4 heures en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

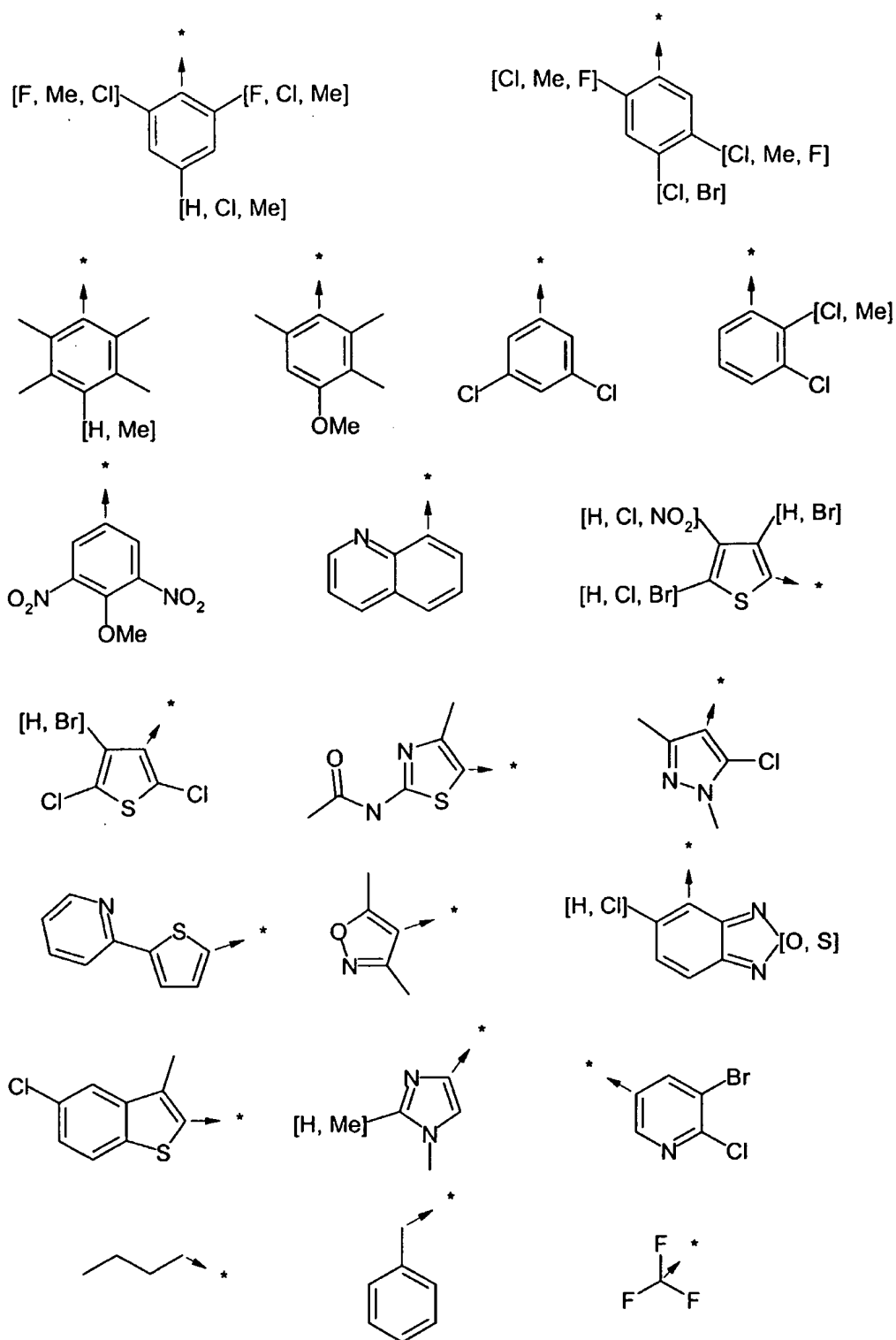
Exemple B3c : Carboxamide de N-(4-bromophénéthyl)-N-(4-pipéridinyl)-2-thiophène ($C_{18}H_{21}BrN_2OS$, $M = 393,3$)



15

55 mg (50 μ mol) de la résine (voir préparation 3) sont prégonflés dans du tétrahydrofurane anhydre. On ajoute ensuite la triéthylamine (42 μ l, 300 μ mol, 6 éq.) puis le chlorure de 2-thiophène carbonyle (37 mg, 250 μ mol, 5 éq.) et le tout est agité toute la nuit. La résine est filtrée, rincée au tétrahydrofurane, à la diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On ajoute 800 μ l d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et on agite 1,5 heure à température ambiante. La résine est filtrée et rincée au dichlorométhane. Le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium. pour obtenir 10 mg d'une huile brune (rdt = 50 %).

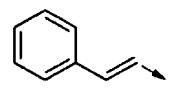
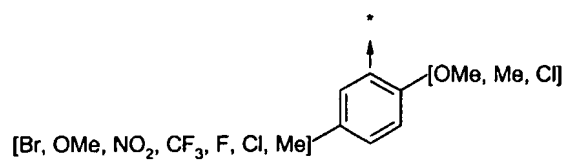
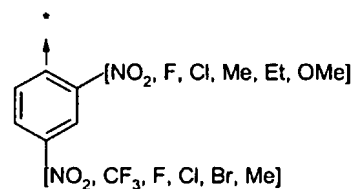
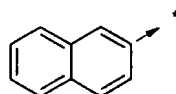
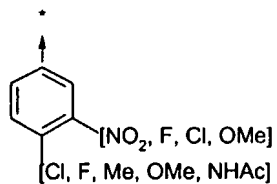
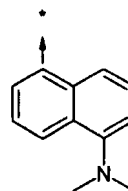
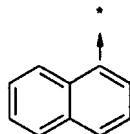
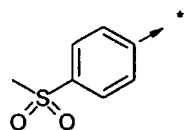
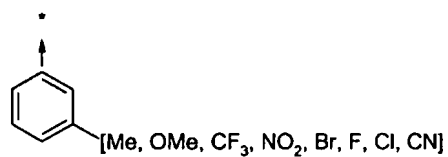
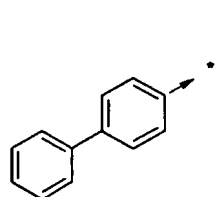
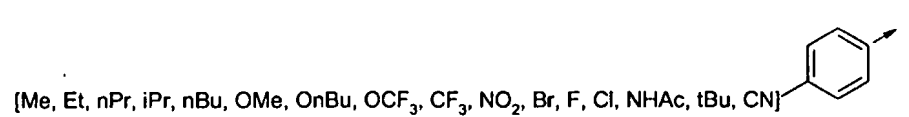
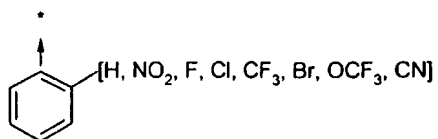
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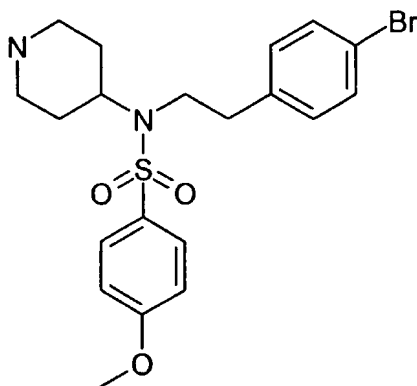
B3c) Fonctionnalisation avec des chlorures d'acides

Elle s'effectue selon le schéma suivant

- 47 -



- 46 -

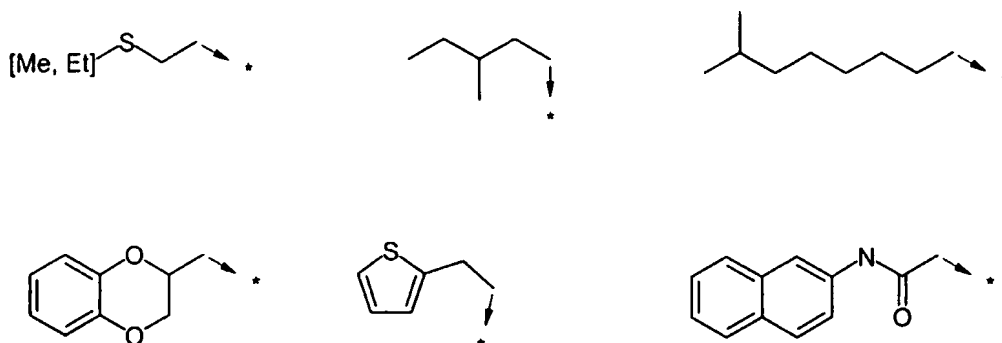


55 mg (50 μ mol) de résine (voir préparation 3) sont prégonflés dans du dichlorométhane anhydre. On ajoute ensuite la triéthylamine (42 μ l, 300 μ mol, 6 équ.) puis le chlorure de 4-méthoxybenzène sulfonyle (51,5 mg, 250 μ mol, 5 équ.) et le tout
5 est agité toute la nuit. La résine est filtrée, rincée au tétrahydrofurane, au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On répète la réaction une seconde fois pour avoir une substitution complète. On ajoute 800 μ l d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et on agite 1,5 heure à température ambiante. La résine est filtrée et
10 rincée au dichlorométhane. Le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium. 14 mg d'une huile brune (rdt = 63 %) ont ainsi été isolés.

RMN ¹H (CD₃OD, 400 MHz) δ : 7,8 (dd, J = 2,8 et 10Hz, 2H); 7,44 (dd, J = 1,2 et 6,8Hz, 2H); 7,17 (d, J = 8,4Hz, 2H); 7,07 (dd, J = 3,2 et 10Hz, 2H); 3,87 (s, 3H, OCH₃); 3,72 (m, 1H); 3,3 (m, 2H); 3,04 (d, J = 12,8Hz, 2H); 2,92 (t, J = 8,4Hz, 2H); 2,6 (t, J = 12,4Hz, 2H); 1,58 (m, 2H); 1,47 (d large, J = 10Hz, 2H). SM/CL : m/z = 455 (M+H).

Une série de sulfonamides a été synthétisée selon cette procédure. Les radicaux R₁ que l'on peut envisager sont ceux illustrés aux points A et B3a ci-dessus. Les
20 radicaux X₃ que l'on peut envisager sont les suivants :

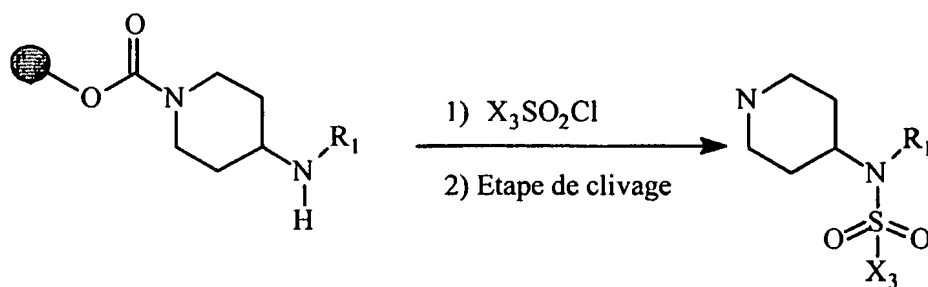
- 45 -



Les radicaux X_1 que l'on peut envisager sont ceux illustrés au point A ci-dessus.

B3b) Fonctionnalisation avec des chlorures de sulfonyles

Elle s'effectue selon le schéma suivant

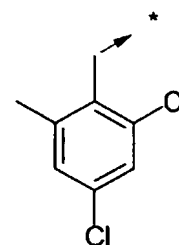
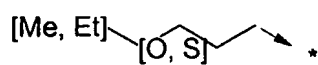
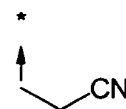
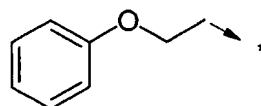
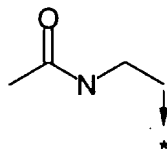
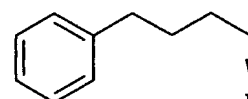
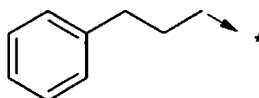
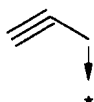
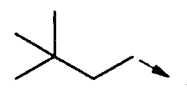
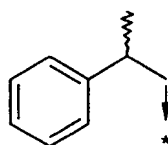
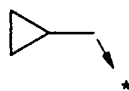
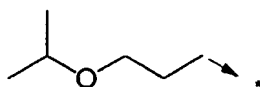
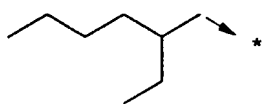
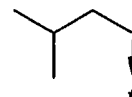
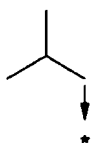
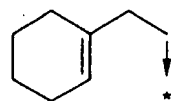
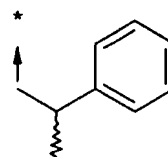
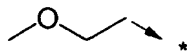
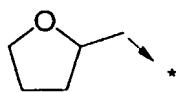


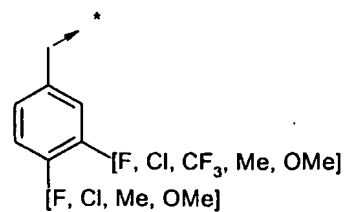
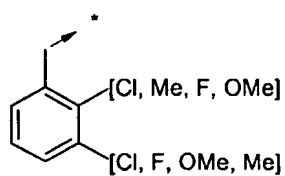
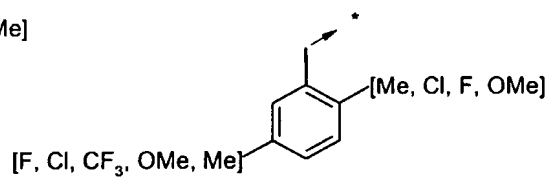
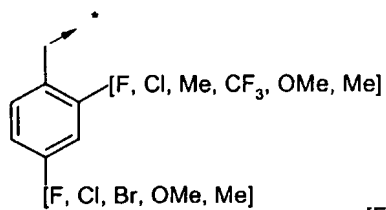
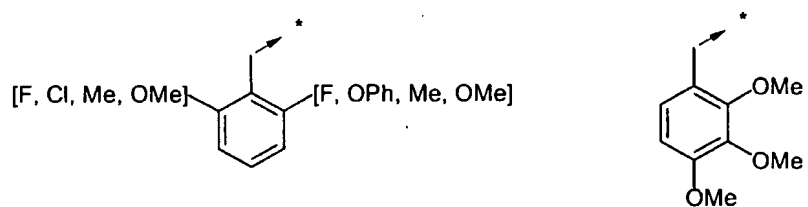
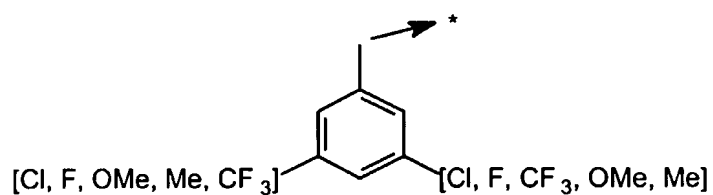
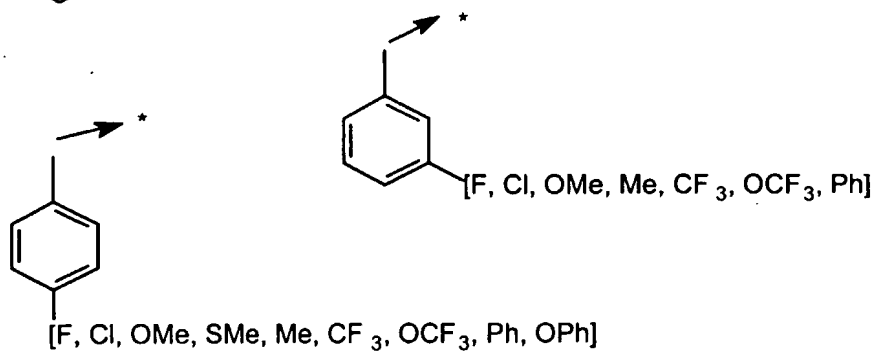
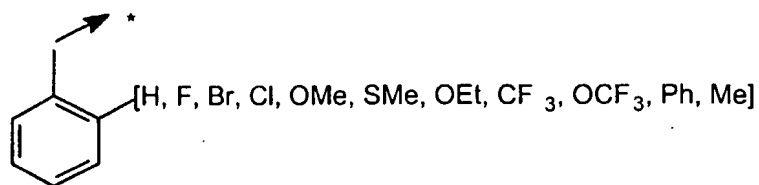
5

Procédure générale : la résine "amine secondaire" est prégonflée dans des solvants comme le dichlorométhane, le diméthylformamide ou le tétrahydrofurane. Puis le chlorure de sulfonyle (5 à 10 éq.) et la triéthylamine (6 à 12 éq.) sont ajoutés et le mélange agité de 12 à 24 heures à température ambiante. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, le diméthylformamide et le tétrahydrofurane, puis séchée sous vide. On agite ensuite la résine de 1 à 4 heures en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

Exemple B3b : Sulfonamide de N-(4-bromophénéthyl)-4-méthoxy-N-(4-pipéridinyl) phényle ($C_{20}H_{25}BrN_2O_3S$, $M = 453,4$)

- 44 -

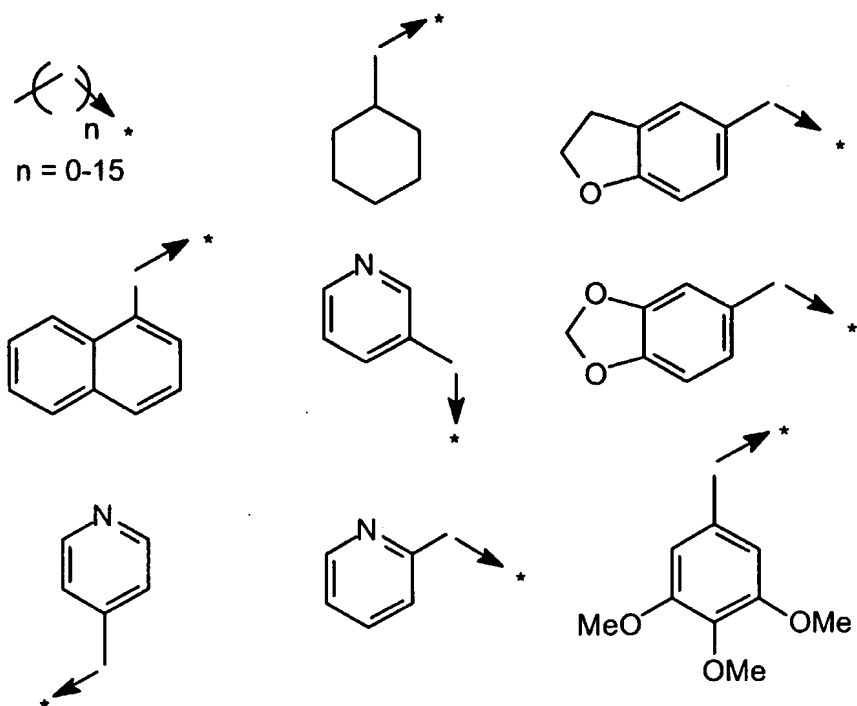




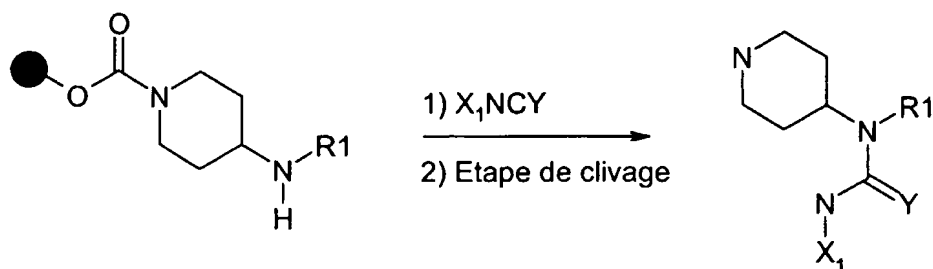
trifluoroacétique. La résine est filtrée et rincée au dichlorométhane, le filtrat est concentré, redilué dans du dichlorométhane et lavé avec une solution saturée de bicarbonate de sodium. 6 mg d'une huile brune (rdt = 25 %) sont ainsi isolés.

RMN ^1H (CD_3OD , 400 MHz) δ : 7,53 (m, 4H); 7,44 (d, $J = 6,8\text{Hz}$, 2H); 7,21 (d, $J = 8,4\text{Hz}$, 2H); 4,1 (m, 1H); 3,53 (t, $J = 7,2\text{Hz}$, 2H); 3,12 (d, $J = 12,8\text{Hz}$, 2H); 2,89 (t, $J = 8\text{Hz}$, 2H); 2,7 (m, 2H); 1,73 (m, 4H). SM/CL : $m/z = 472,2$ (M+H).

Une série d'urées ($Y = O$) et de thiourées ($Y = S$) a été synthétisée selon cette procédure. Les radicaux R_1 que l'on peut envisager sont les suivants :



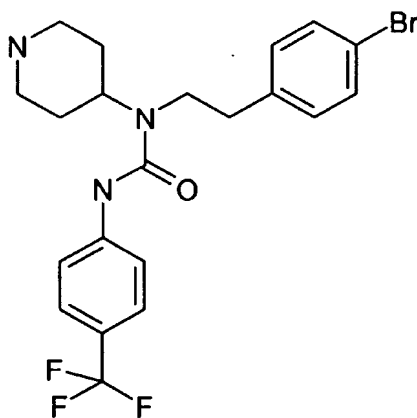
- 40 -



La procédure générale est la suivante : la résine "amine secondaire" est prégonflée dans un solvant tel que le dichlorométhane ou le diméthylformamide avant l'addition d'isocyanate ou d'isothiocyanate (3 à 10 éq.). Le mélange est agité 1 à 24 heures à température ambiante. La résine est alors filtrée, lavée avec des solvants tels que le dichlorométhane, le diméthylformamide et le tétrahydrofurane puis séchée sous vide.

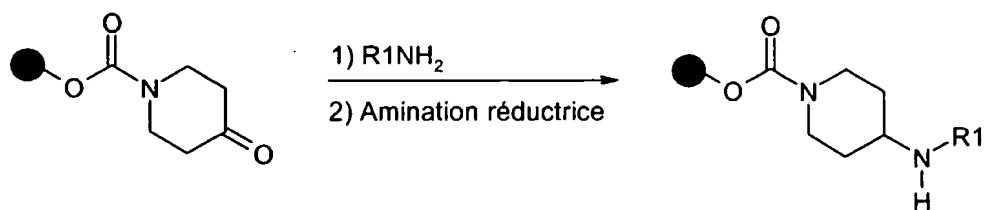
Le clivage de la résine s'effectue en présence d'un mélange équimolaire de dichlorométhane et d'acide trifluoroacétique et une agitation de 30 minutes à 4 heures. La résine est rincée au dichlorométhane puis le filtrat est concentré sous vide. Dans certains cas le filtrat est redissout dans du dichlorométhane puis désalifié avec une solution saturée de carbonate de sodium. La phase organique est évaporée sous vide pour donner la base libre.

Exemple B3a : Urée de N-(4-bromophénéthyl)-N-(4-pipéridinyl)-N'-[4-(trifluorométhyl) phényl] ($\text{C}_{21}\text{H}_{23}\text{BrF}_3\text{N}_3\text{O}$, $M = 470,3$)



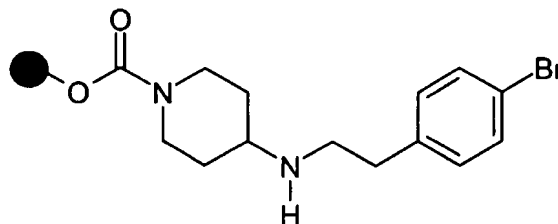
15

55 mg (50 μmol) de la résine (voir préparation 3) sont prégonflés dans du dichlorométhane anhydre. On ajoute ensuite le 4-trifluorophénylisocyanate (28 mg, 150 μmol , 3 éq.) et le tout est agité toute la nuit. La résine est filtrée, rincée au tétrahydrofurane, au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide. On agite ensuite 1,5 heure en présence de 800 μl d'un mélange équimolaire de dichlorométhane et d'acide



La procédure générale est la suivante : à la résine cétonique prégonflée dans le triméthylorthoformiate (TMOF) est ajoutée l'amine primaire (5 à 10 éq.) puis le mélange est soniqué. On ajoute ensuite le complexe de borane pyridine (8 M, 5 à 10 éq.) et le mélange est agité 12 à 72 heures. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, la diméthylformamide et le tétrahydrofurane puis séchée sous vide (Pelter, A.; Rosser, R.M. *J. Chem. Soc. Perkin Trans I* **1984**, 717-720 ; Bomann, M.D.; Guch, I.C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995-5996 ; Khan, N.M.; Arumugam, V.; Balasubramanian, S. *Tetrahedron Lett.* **1996**, *37*, 4819-4822).

Préparation 3



300 mg (taux de charge de 0,88 mmol/g, 0,27 mmol) de résine cétonique sont prégonflés dans le TMOF. On ajoute ensuite la 4-bromophénéthylamine (540 mg, 420 μl , 2,7 mmol, 10 éq.) puis le complexe de borane pyridine (8 M, 338 μl , 2,7 mmol, 10 éq.). Le mélange est agité 56 heures à température ambiante. La résine est filtrée, rincée successivement avec du dichlorométhane, du diméthylformamide, du tétrahydrofurane et du dichlorométhane puis séchée sous vide. 340 mg de résine jaune pâle sont ainsi obtenus avec un taux de charge de 0,81 mmol/g calculé d'après l'analyse élémentaire de l'azote.

B3) Fonctionnalisation

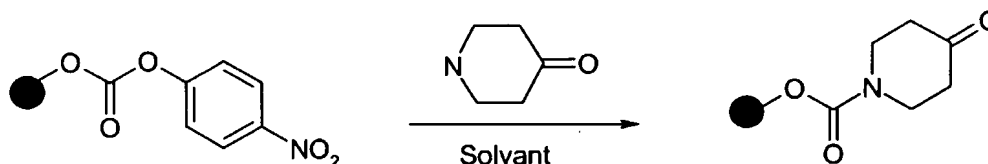
B3a) Fonctionnalisation avec des isocyanates ou des isothiocyanates

Elle s'effectue selon le schéma

du dichlorométhane ou du tétrahydrofurane à température ambiante. Le mélange est agité toute la nuit. La résine est lavée avec du tétrahydrofurane, du diéthyléther et du dichlorométhane puis séchée *in vacuo* à 50° C toute la nuit.

B1b) Préparation de la résine carbamate de pipéridone

- 5 Elle s'effectue selon le schéma suivant



- 10 Au chlorhydrate hydraté de pipéridone dilué dans de la diméthylformamide est ajoutée de la triéthylamine (1 éq.) et du tamis moléculaire. Le mélange est chauffé jusqu'à dissolution complète de la cétone. Cette solution est ajoutée à la résine carbonate de *p*-nitrophényle de Wang (0,05 éq.) prégonflée dans la diméthylformamide. Après 24 à 72 heures d'agitation à température ambiante, la résine est filtrée puis lavée plusieurs fois avec de la diméthylformamide, du tétrahydrofurane, du diéthyléther et du dichlorométhane.

15 **Préparation 2**

- 2,5 g de la résine carbonate de *p*-nitrophényle de Wang (taux de charge de 0,88 mmol/g, 2,2 mmol) est prégonflée dans 100 ml de diméthylformamide. Dans le même temps, 6,7 g (44 mmol, 20 éq.) de chlorhydrate hydraté de pipéridone, 4,45 g (44 mmol, 20 éq.) de triéthylamine et trois spatules de tamis moléculaire sont chauffés dans 100 ml de diméthylformamide jusqu'à dissolution complète. La solution jaunâtre est versée chaude sur la résine et le mélange agité 40 heures à température ambiante. La résine est filtrée puis lavée avec de la diméthylformamide, du tétrahydrofurane, du diéthyléther et du dichlorométhane (3 fois chaque solvant) puis séchée sous vide. 2,4 g de résine jaune pâle sont isolés avec un taux de charge de 0,88 mmol/g calculé d'après l'analyse élémentaire de l'azote.

B2) Amination réductrice sur support solide

Elle s'effectue selon le schéma suivant :

dans le dichlorométhane est ajouté 1,6 ml (21 mmol, 20 éq.) d'acide trifluoroacétique. La réaction est agitée 90 minutes puis concentrée. Du dichlorométhane est ajouté et la phase organique est lavée avec une solution saturée de bicarbonate de sodium, séchée sur sulfate de magnésium, filtrée et concentrée sous vide pour isoler 490 mg (rdt = 98 %) d'une mousse blanche.

RMN ^1H (CD_3OD , 400 MHz) δ : 7,7 (s, 1H) ; 7,55 (d, 1H) ; 7,44 (t, 1H) ; 7,28 (m, 9H) ; 7,18 (m, 2H) ; 4,05 (m, 2H) ; 3,26 (m, 2H) ; 3,11 (d, $J = 10,8\text{Hz}$, 2H) ; 2,7 (td, $J = 2,4$ et $12,4\text{Hz}$, 2H) ; 2,38 (q, $J = 8\text{Hz}$, 2H) ; 1,76 (d, $J = 10\text{Hz}$, 2H) ; 1,63 (qd, $J = 4$ et $12,4\text{Hz}$, 2H). SM/CL : $m/z = 482,2$ ($\text{M}+\text{H}$).

10 Une série de 4-aminopipéridines a été synthétisée selon cette procédure. Les radicaux R_1 , X_1 et X_2 que l'on peut envisager sont ceux déjà illustrés aux points A1 et A2 ci-dessus.

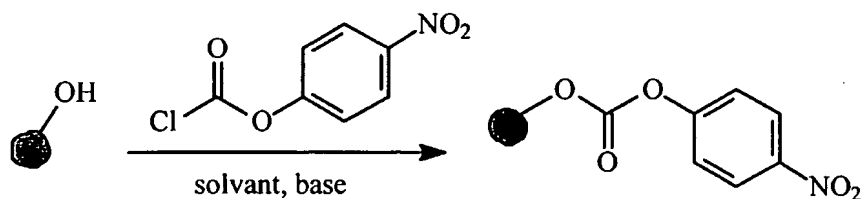
B) Synthèse en phase solide de 4-aminopipéridines

Des 4-aminopipéridines ont été préparées par synthèse en phase solide en partant de la résine de Wang.

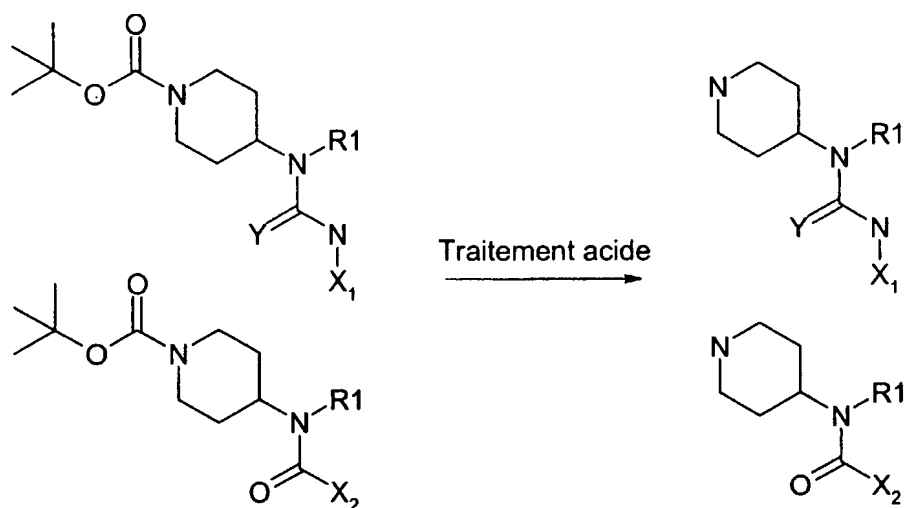
B1) Préparation de la résine

B1a) Préparation de la résine carbonate de *p*-nitrophényle de Wang

Elle s'effectue selon le schéma suivant



20 Cette résine a été préparée à partir de la résine de Wang (fournie par Bachem ou Novabiochem) avec des taux de charge supérieurs à 0,89 mmol/g, suivant la procédure décrite dans la littérature (Bunin, B.A. *The Combinatorial Index*, Academic Press, 1998, p. 62-63 ; Dressman, B.A. ; Spangle, L.A. ; Kaldor, S.W. *Tetrahedron Lett.* 1996, 37, 937-940 ; Hauske, J.R. ; Dorff, P. *Tetrahedron Lett.* 1995, 36, 1589-1592 ; Cao, J. ; Cuny, G.D. ; Hauske, J.R. *Molecular Diversity* 1998, 3, 173-179) : de la N-méthylmorpholine ou de la pyridine et du chloroformate de 4-nitrophényle sont successivement additionnés à la résine de Wang prégonflée dans

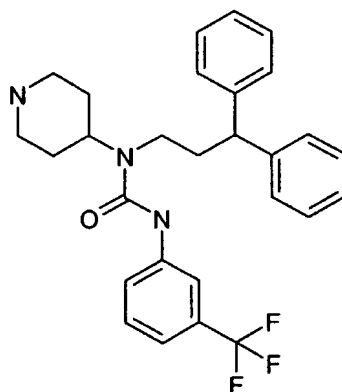


Procédure générale : deux méthodes ont été utilisées pour effectuer la déprotection en milieu acides des urées, thiourées et amides précédemment décrits. La première

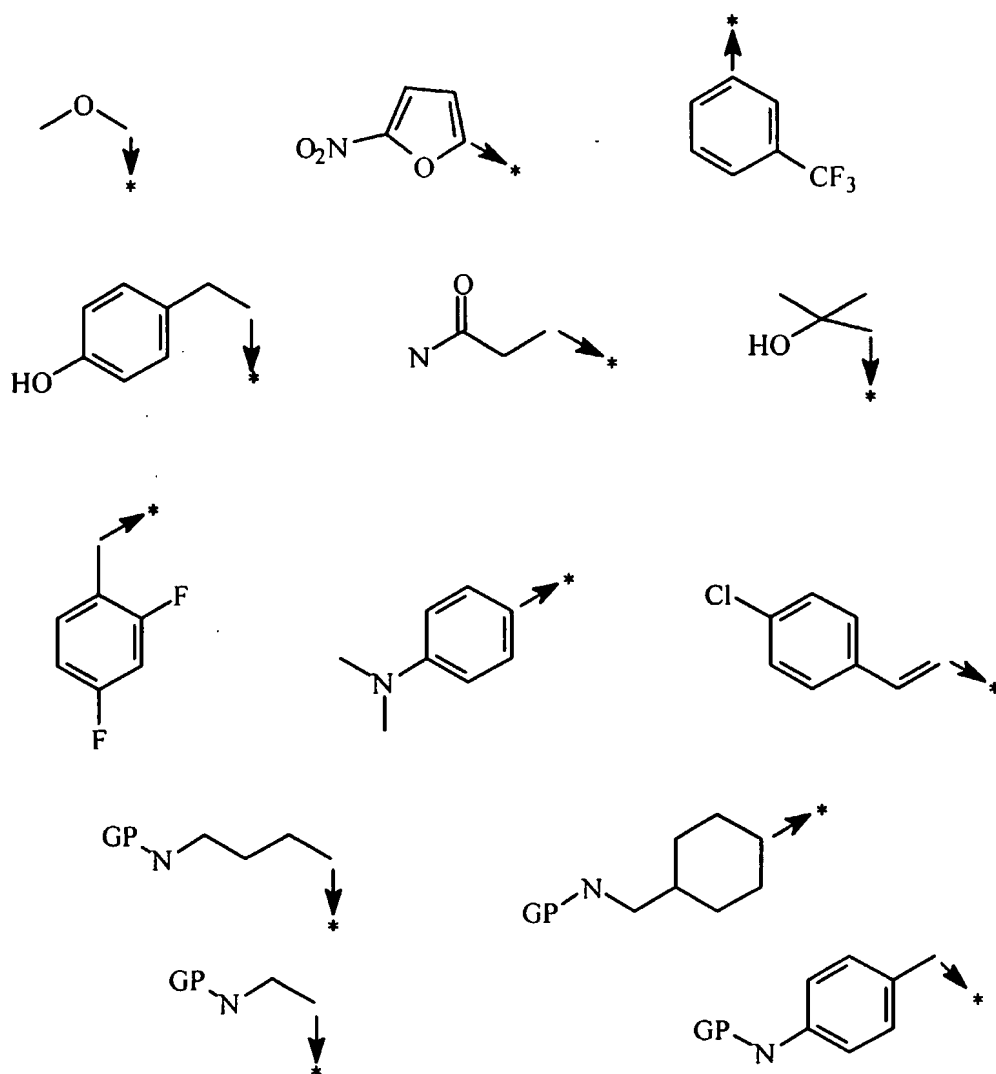
5 consiste à dissoudre le composé dans du dichlorométhane et additionner l'acide trifluoroacétique (5 à 20 équ.) tandis que dans la seconde une solution d'acide chlorhydrique dilué dans des solvants tels que l'acétate d'éthyle, le dioxane ou le diéther (5 à 20 équ.) est utilisée. La réaction est agitée 1 à 4 heures à température ambiante. Dans certains cas, du dichlorométhane est ajouté et la phase organique est

10 lavée avec une solution saturée de bicarbonate de sodium, séchée sur sulfate de magnésium, filtrée et concentrée sous vide pour isoler la base libre.

Exemple A3 : Urée de N-(3,3-diphénylpropyl)-N-(4-pipéridinyl)-N'-[3-(trifluorométhyl)phényl] ($C_{28}H_{30}F_3N_3O$, M = 481,57)



15 A une solution de carboxylate de *tert*-butyl 4-((3,3-diphénylpropyl) {3-(trifluorométhyl)anilino}carbonyl)amino)-1-pipéridine (600 mg, 1,04 mmol)

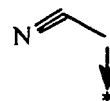
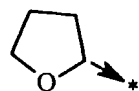
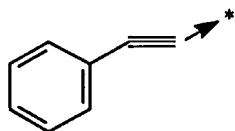
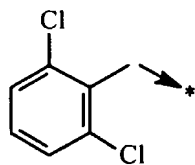
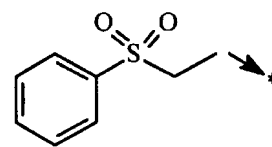
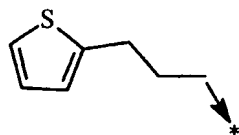
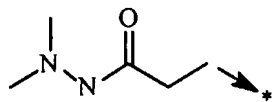
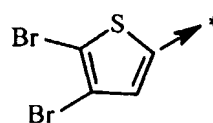
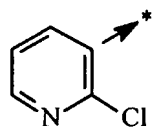
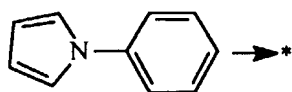
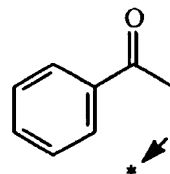
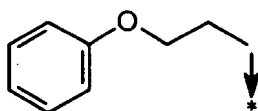
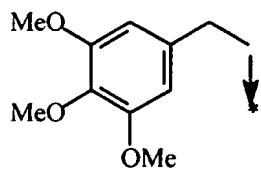
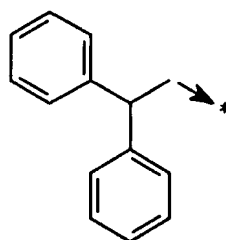
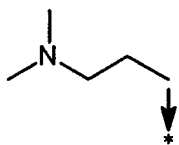
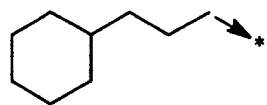


où le groupe protecteur (GP) représente H ou *tert*-butyloxycarbonyle.

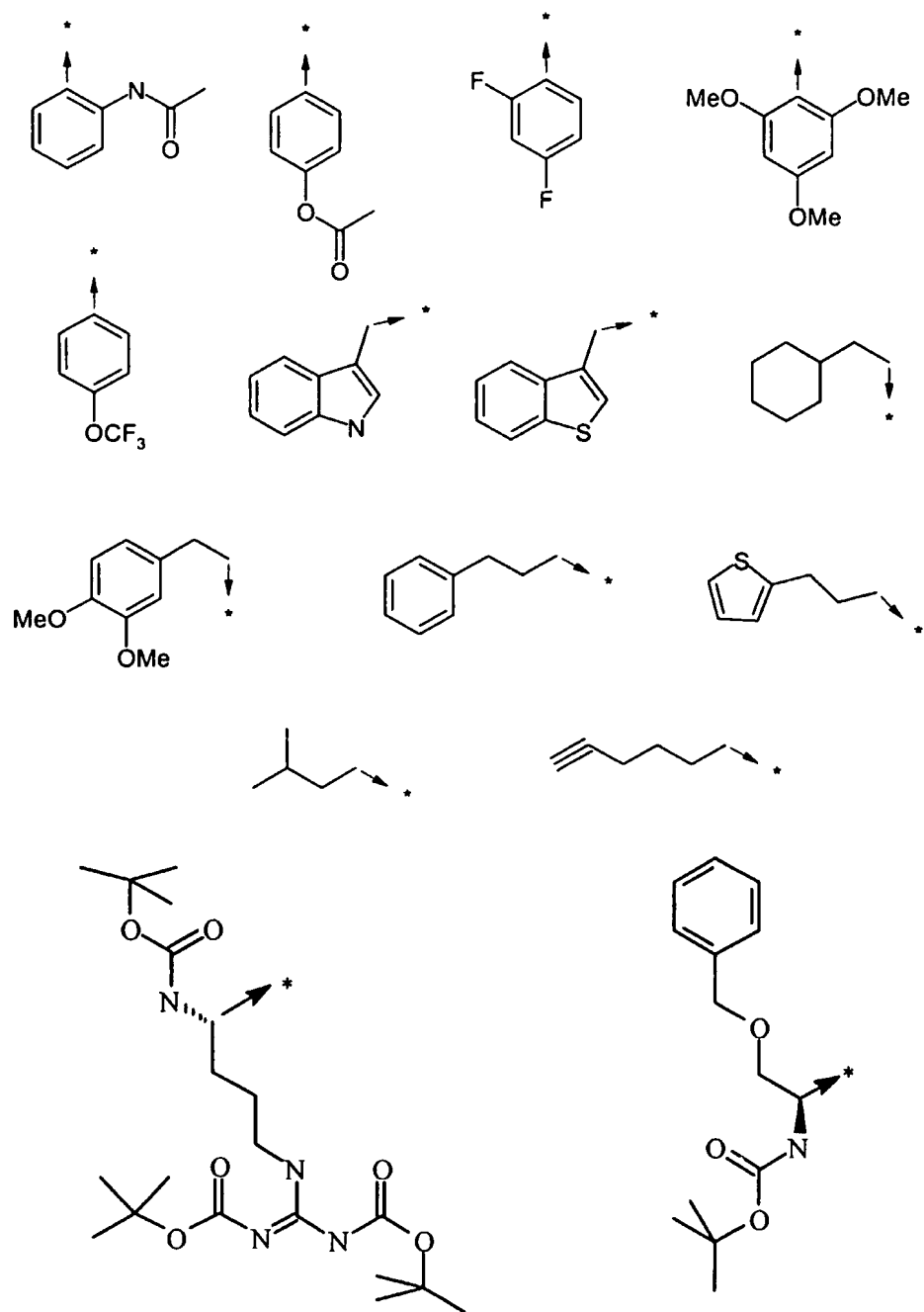
A3) Synthèses de pipéridines 4-aminodisubstituées

La synthèse des pipéridines 4-aminodisubstituées selon l'invention, peut s'effectuer
 5 par traitement acide des composés N-Boc précédemment décrits, suivant le schéma réactionnel suivant :

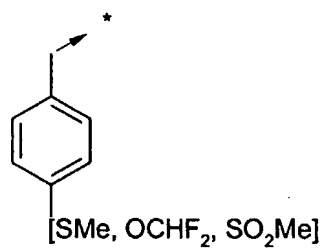
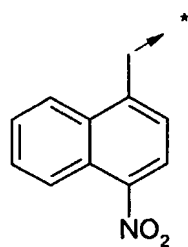
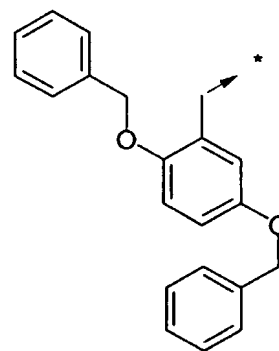
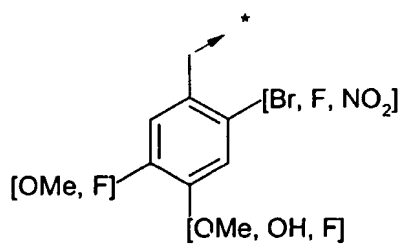
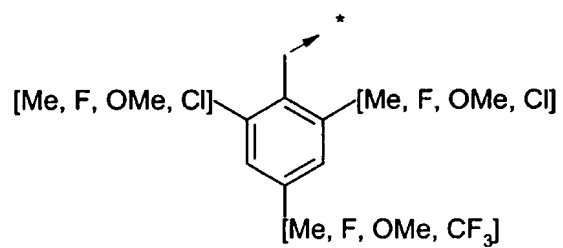
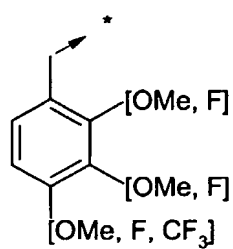
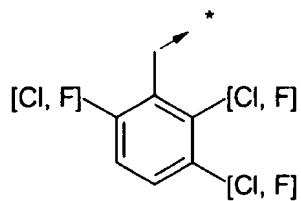
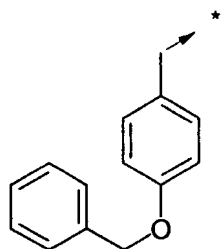
- 34 -



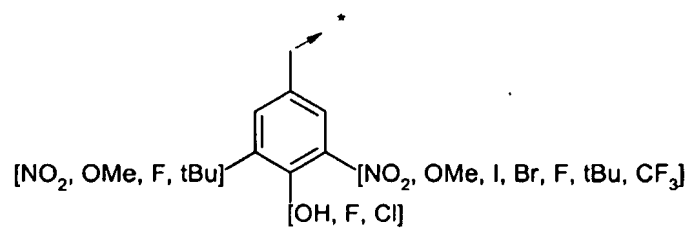
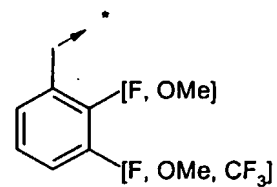
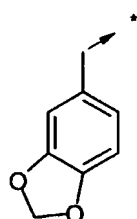
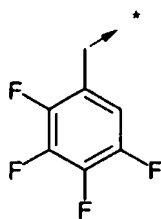
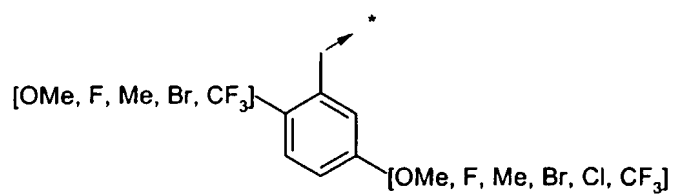
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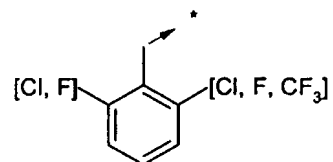
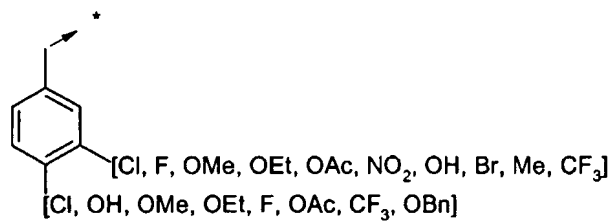
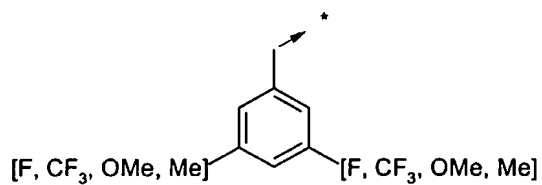
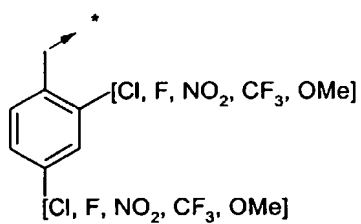
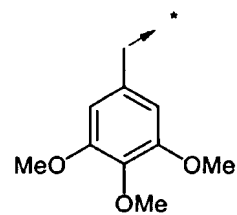
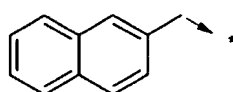
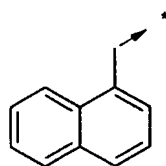
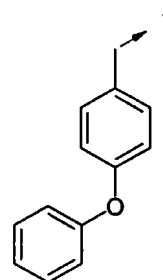
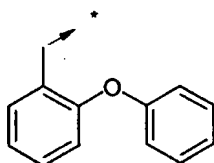
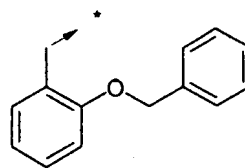
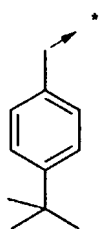
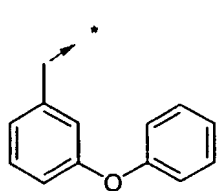
- 32 -



- 31 -

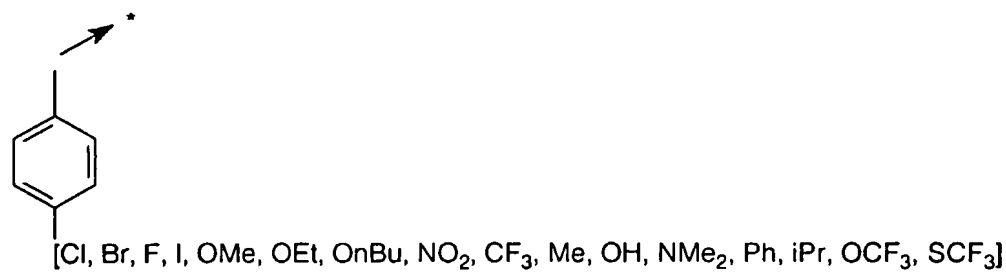
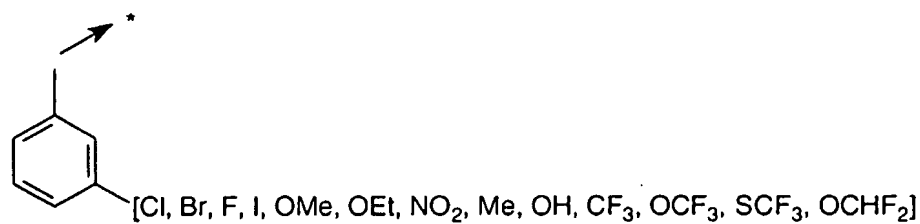
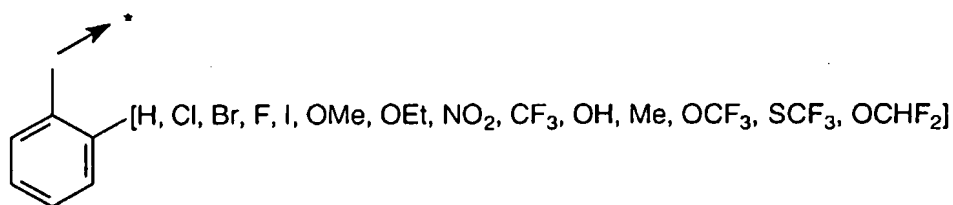


- 30 -



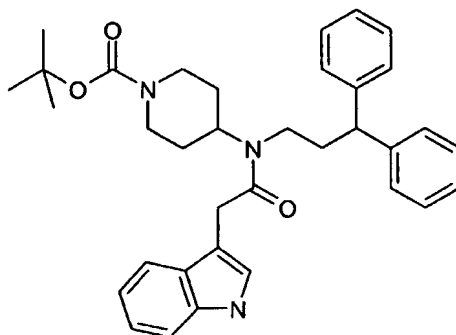
1H) ; 2,26 (m, 3H) ; 1,6 (m, 2H) ; 1,44 (s, 9H) ; 1,13 (m, 2H). SM/CL : $m/z = 552,4$ (M+H).

Une série d'amides a été synthétisée selon cette procédure. Les radicaux X_2 que l'on peut envisager sont les suivants :



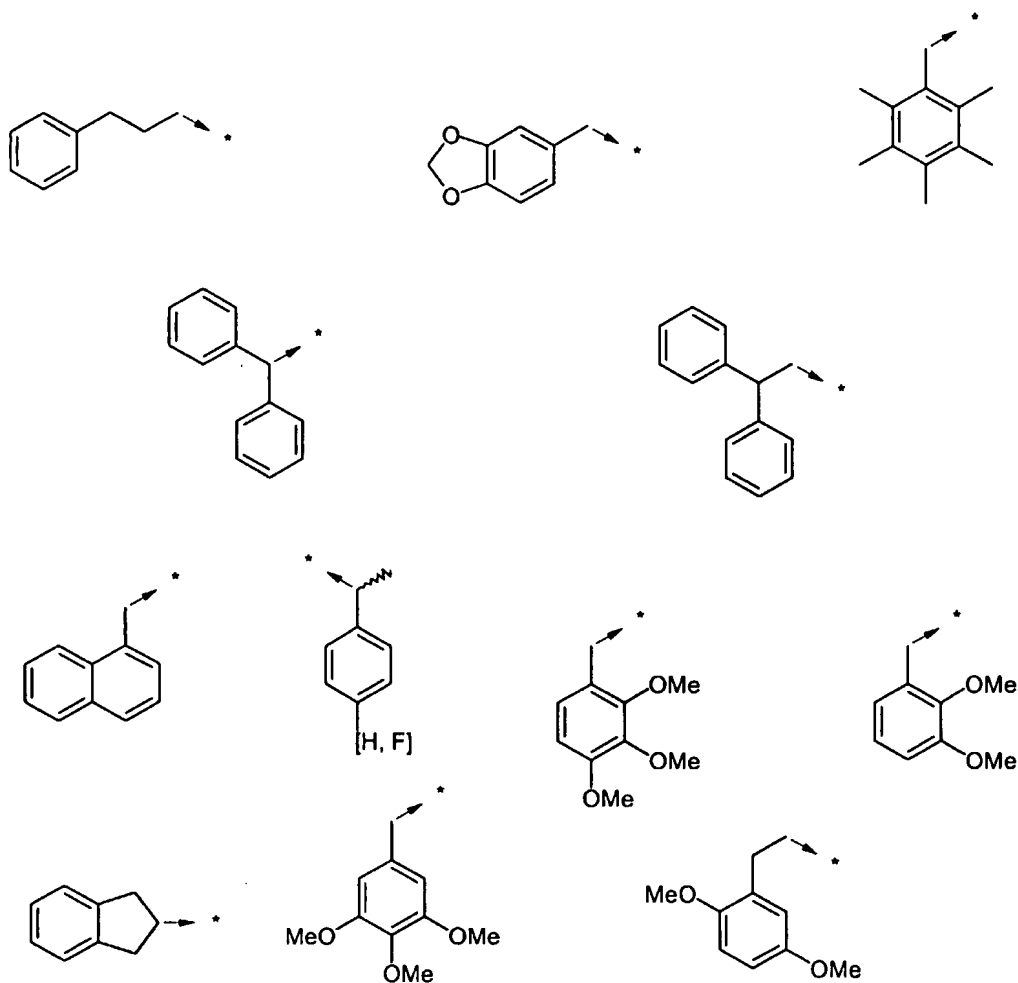
La procédure générale est la suivante : l'acide carboxylique (1,1 à 2,5 éq.) dissout dans un solvant aprotique anhydre tel que le dichlorométhane, la diméthylformamide ou le tétrahydrofurane est activé avec du 1-éthyl-3-(3-diméthylaminopropyl) carbodiimide greffé sur résine (P-EDC, Novabiochem, 2,33 mmol/g, 1,3 à 3 éq.) (Desai, M.C. ; Stephens Stramiello, L.M. *Tetrahedron Lett.* **1993**, 34, 7685-7688). Ce mélange est agité 5 à 30 minutes à température ambiante. La 4-aminosubstitué-1-pipéridine prédissoit dans un solvant aprotique anhydre tel que le dichlorométhane, la diméthylformamide ou le tétrahydrofurane est alors ajouté et le mélange réactionnel agité à température ambiante 1 à 18 heures. Dans certains cas, de la résine basique échangeuse d'ions (IRA-68, SAX) est ajoutée et le mélange à nouveau agité à température ambiante 1 à 18 heures. Les résines sont filtrées sur fritté ou sur cartouche de résine basique échangeuse d'ions (IRA-68, SAX) ou sur cartouche d'alumine basique (500 mg, Interchim).

Exemple A2b : Carboxylate de *tert*-butyl 4-[(3,4-diméthoxyphénéthyl)[2-(1H-indol-3-yl)acétyl]amino]-1-pipéridine (C₃₅H₄₁N₃O₃, M = 551,74)



512 mg (1,12 mmol, 1,4 éq.) de résine P-EDC est prégonflée dans le dichlorométhane. L'acide 2-(1H-indol-3-yl)acétique (153 mg, 0,875 mmol, 1,1 éq.) est ajouté et le mélange agité 10 minutes. Le carboxylate de *tert*-butyl 4-[(3,3-diphénylpropyl)amino]-1-pipéridine (292 mg, 0,8 mmol) dans le tétrahydrofurane est ajouté et la réaction agitée toute la nuit. 2 spatules de résine basique échangeuse d'ions IRA-68 sont ajoutées et la réaction agitée à nouveau toute la nuit. Les résines sont filtrées et le filtrat est concentré sous vide pour donner 250 mg (rdt = 86 %) d'une mousse jaune pâle.

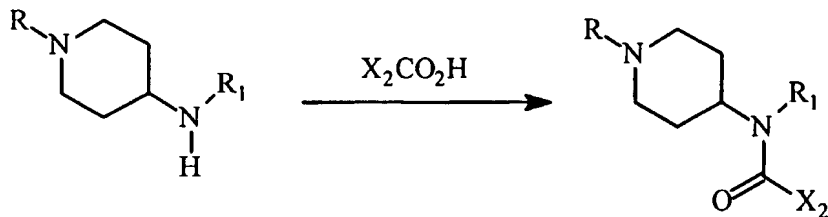
RMN ¹H (CD₃OD, 400 MHz) δ : 7,63 (d, J = 8Hz, 1H) ; 7,44 (d, J = 8Hz, 1H) ; 7,36 (d, J = 8Hz, 1H) ; 7,26 (d, J = 8Hz, 1H) ; 7,2 (m, 6H) ; 7,13 (m, 3H) ; 7,1 (m, 2H) ; 6,68 (s, 1H) ; 4-3,75 (m, 4H) ; 3,65 (s, 1H) ; 3,2 (m, 1H) ; 3 (m, 1H) ; 2,75 (m,



A2b) Synthèse d'amides à partir d'acides carboxyliques

Les synthèses d'amides à partir d'acides carboxyliques sont mises en œuvre selon le schéma réactionnel suivant :

5



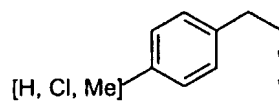
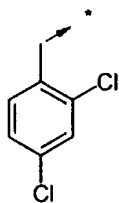
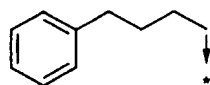
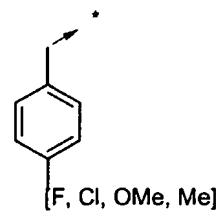
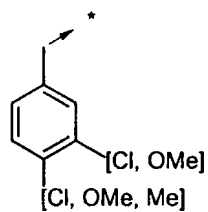
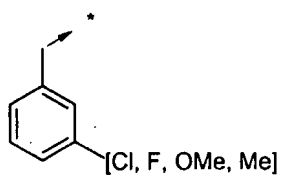
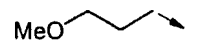
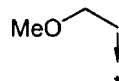
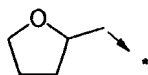
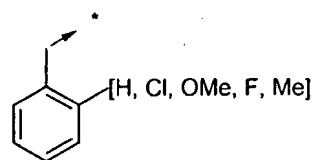
dans laquelle R représente méthyle ou Boc et X_2 a la signification indiquée ci-dessus.

Il est à noter que dans le cas où R représente Boc, le produit ainsi obtenu est un produit final répondant à la formule I selon l'invention mais peut également être

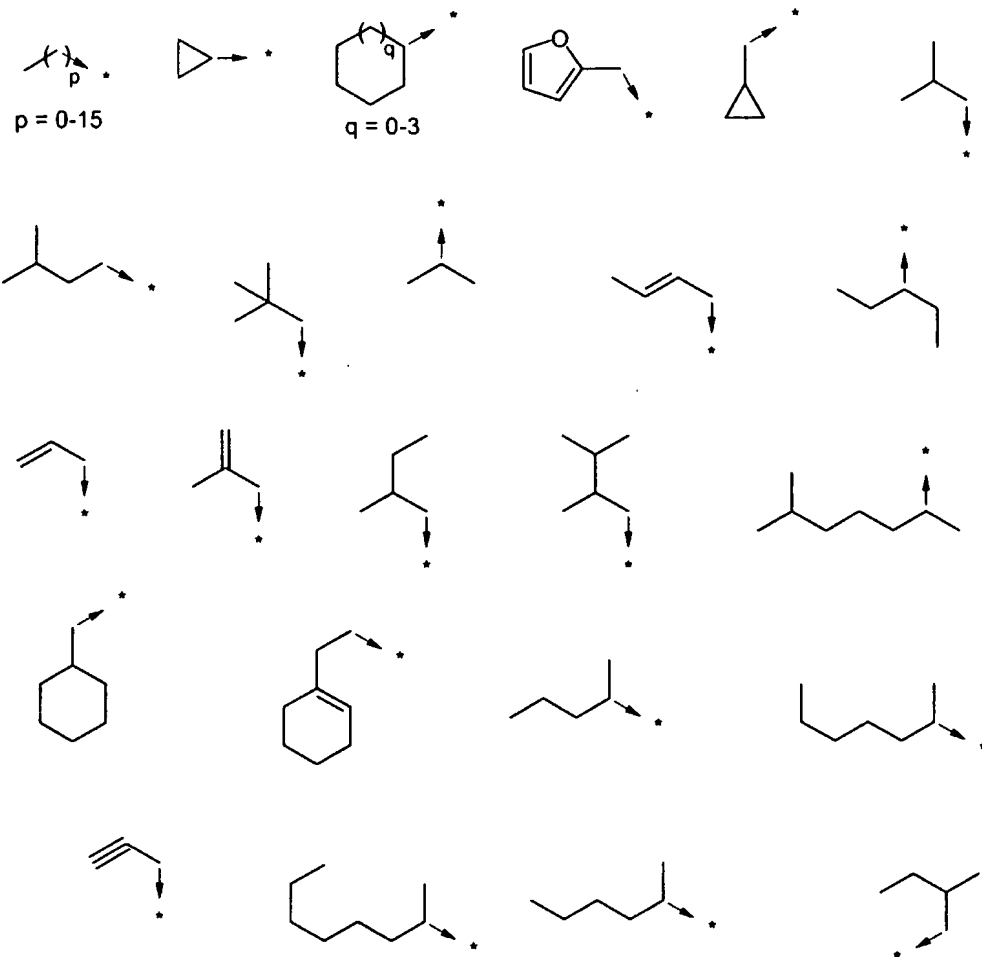
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utilisé comme intermédiaire de synthèse.

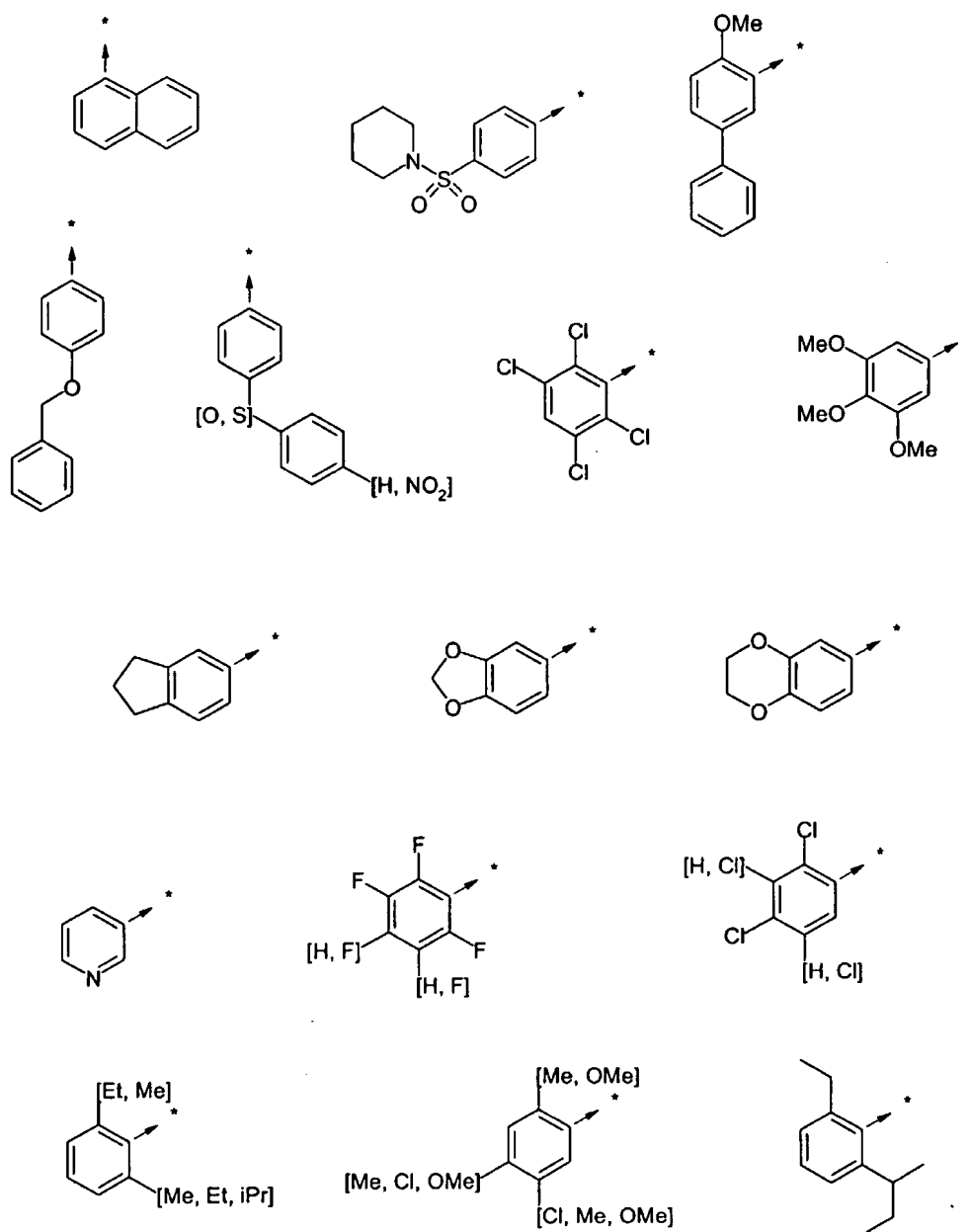
- 26 -



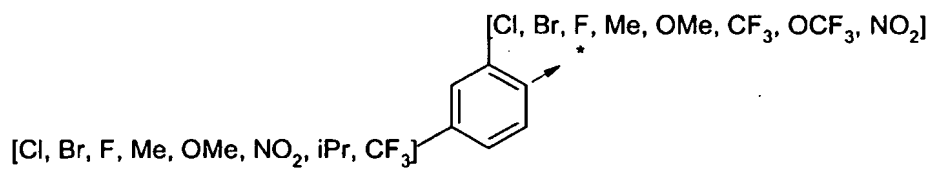
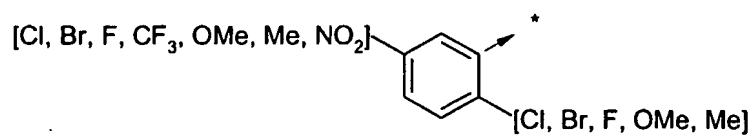
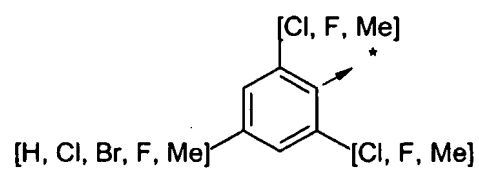
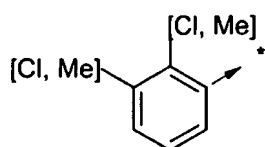
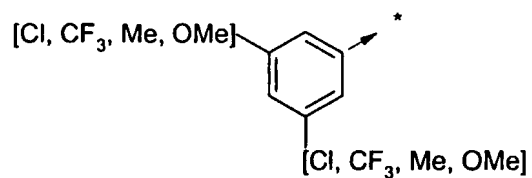
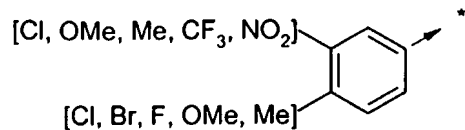
- 25 -



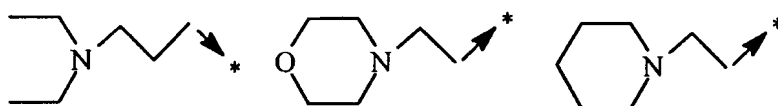
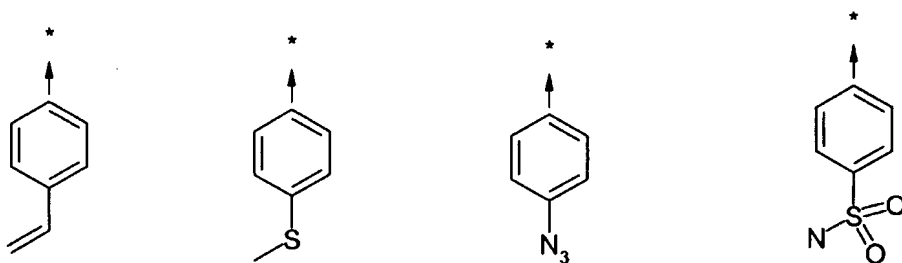
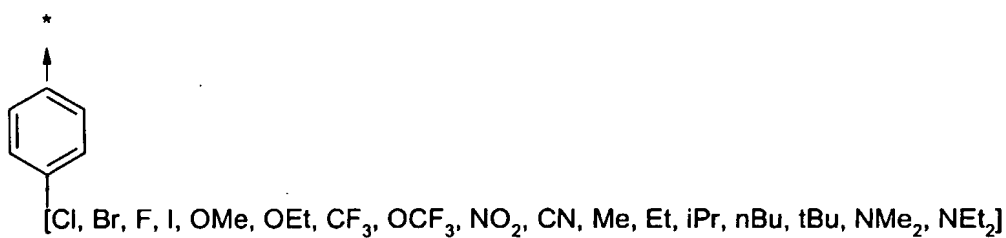
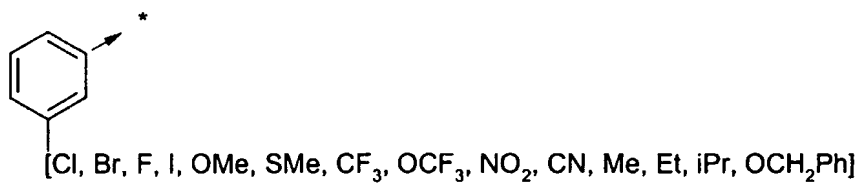
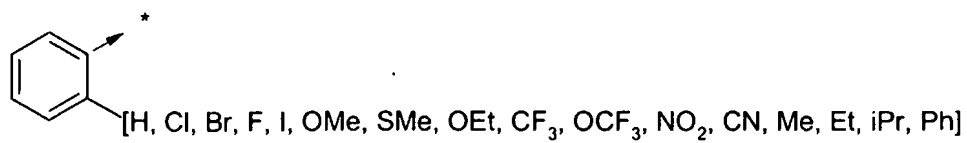
- 24 -



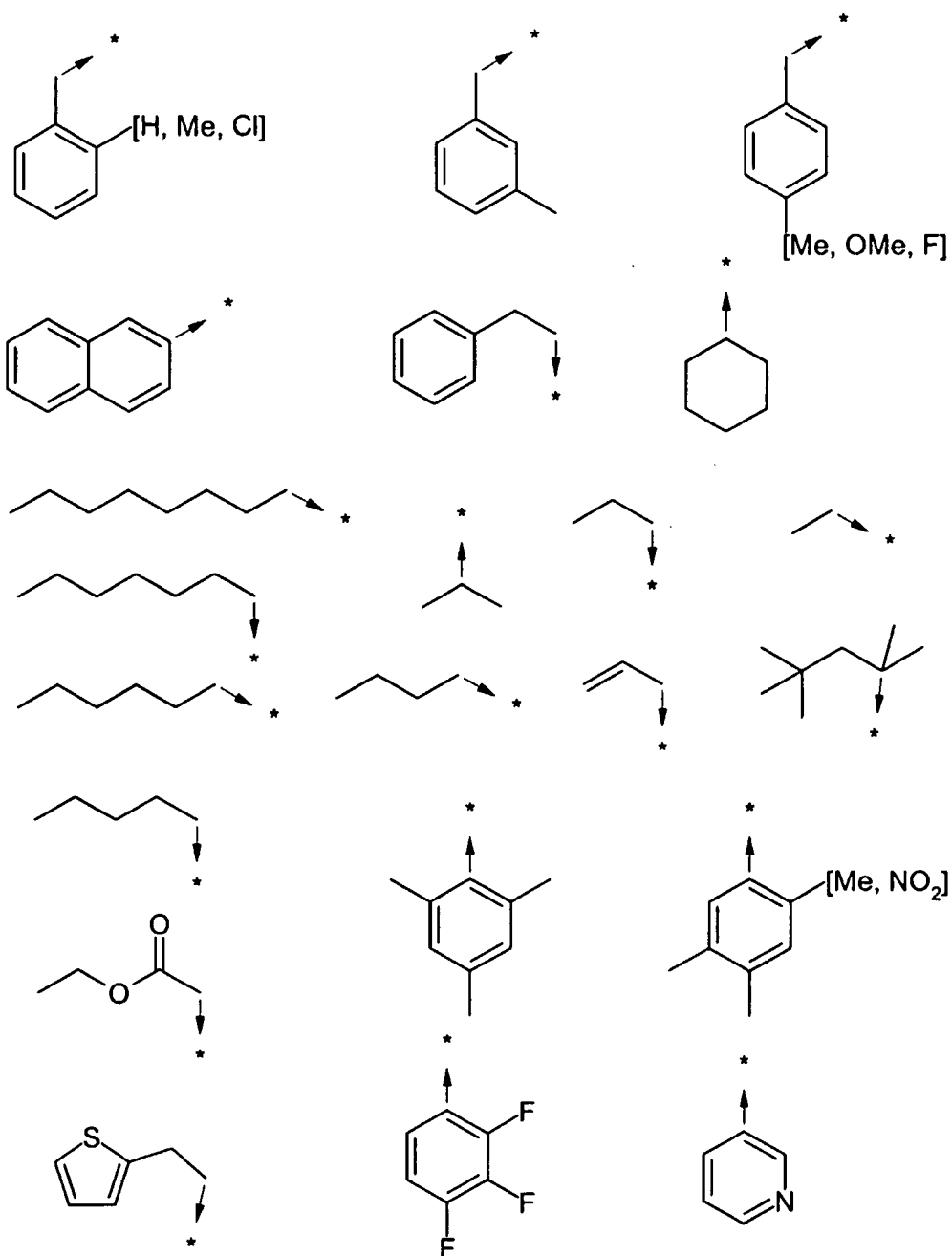
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- 22 -

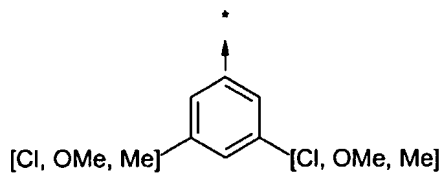
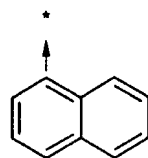
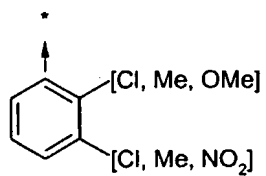
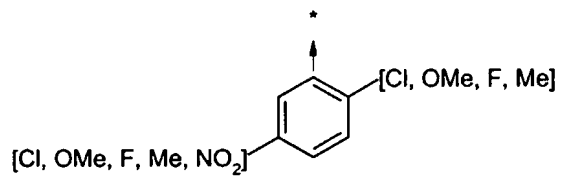
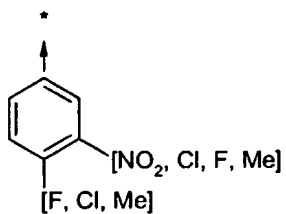
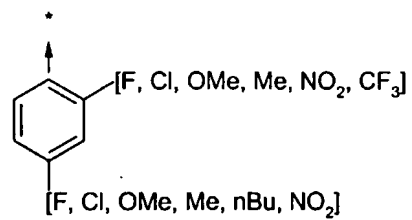
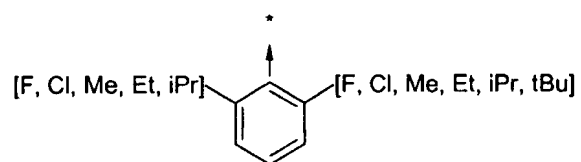


- 21 -



Pour les groupes R_1 tels qu'illustrés au point A1 ci-dessus, les groupes X_1 que l'on peut envisager pour la synthèse de thiourées ($Y = S$) selon la procédure ci-dessus, sont les suivants :

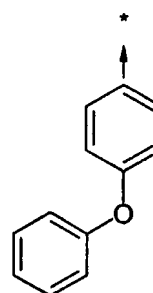
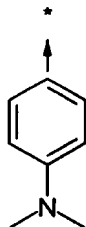
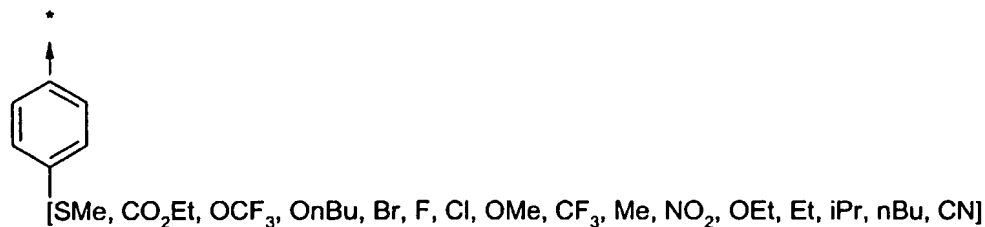
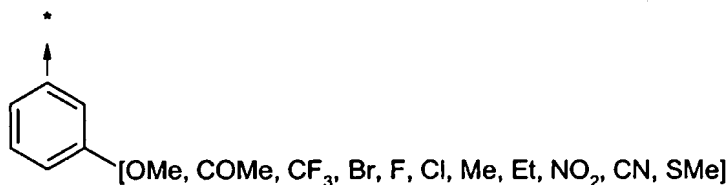
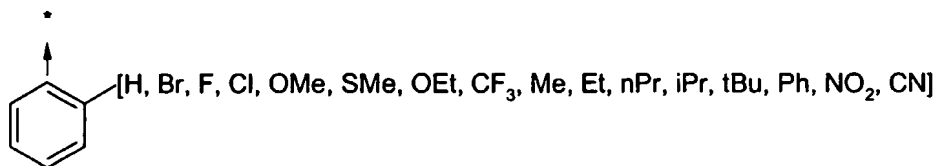
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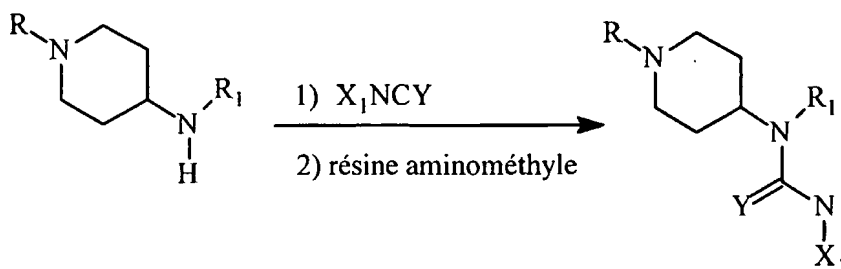


45 minutes, et la résine aminométhyle (180 mg, 0,36 mmol) est ajoutée et la réaction remise sur l'agitateur orbital pendant 45 minutes. La résine est filtrée et lavée au dichlorométhane. Le filtrat est concentré *in vacuo* pour donner 610 mg (rdt = 87 %) d'une mousse blanche.

- 5 RMN ^1H (CD_3OD , 400 MHz) δ : 7,71 (s, 1H) ; 7,57 (d, 1H) ; 7,43 (t, 1H) ; 7,26 (m, 10H) ; 7,15 (m, 1H) ; 4,1 (m, 3H) ; 3,97 (dd, $J = 7,6$ et 10Hz, 1H) ; 3,17 (m, 2H) ; 2,75 (m, 2H) ; 2,35 (m, 2H) ; 1,65 (d, $J = 12\text{Hz}$, 2H) ; 1,46 (s, 9H, groupe *t*butyle) ; 1,39 (dd, $J = 2,4$ et 10,8Hz, 2H) ; 1,29 (s, 1H). SM/CL : $m/z = 582$ (M+H).

- 10 Pour les groupes R_1 tels qu'illustrés au point A1 ci-dessus, les groupes X_1 que l'on peut envisager pour la synthèse d'urées ($Y = O$) selon la procédure ci-dessus, sont les suivants :



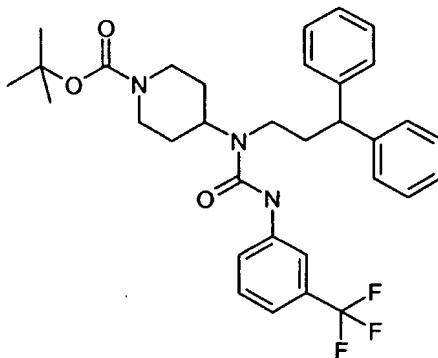


dans laquelle R représente méthyle ou Boc et X_1 et Y ont la signification indiquée ci-dessus. Il est à noter que dans le cas où R représente Boc, le produit ainsi obtenu est un produit final répondant à la formule I selon l'invention mais peut également être utilisé comme intermédiaire de synthèse.

La procédure générale est la suivante : l'isocyanate ou l'isothiocyanate (1,1 à 1,5 éq.) est ajouté à la 4-aminosubstitué-1-pipéridine dans des solvants aprotiques tels que le dichlorométhane, le tétrahydrofurane ou la diméthylformamide et le mélange est agité de 45 minutes à 18 heures à température ambiante. La résine aminométhyle (Novabiochem, 1,33 mmol/g, 0,2 à 1 éq.) est ajoutée et le mélange agité de 45 minutes à 18 heures. Dans certains cas, de la résine basique échangeuse d'ions telle que la IRA-68 (Gayo, L.M. ; Suto, M.J. *Tetrahedron Lett.* **1997**, *38*, 513-516) peut être ajoutée. Les résines sont filtrées et le filtrat concentré. D'autres purifications sur cartouche de gel de silice ou d'alumine basique (500 mg, Interchim) peuvent éventuellement être réalisées.

Exemple A2a : Carboxylate de *tert*-butyl-4-((3,3-diphénylpropyl) {[3-(trifluorométhyl) anilino] carbonyl} amino)-1-pipéridine

($C_{33}H_{38}F_3N_3O_3$, M = 581,68)

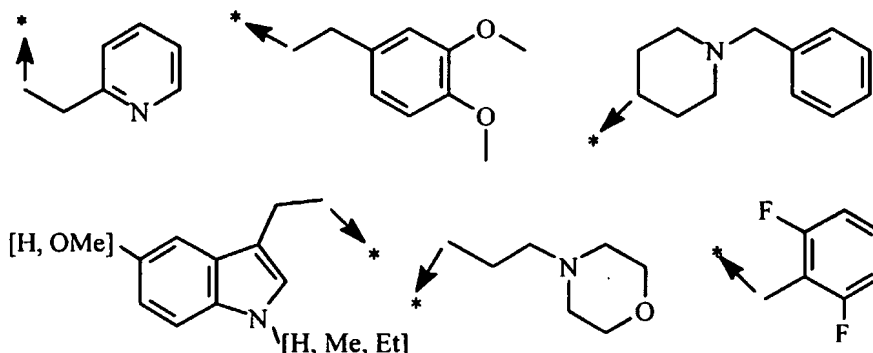


A une solution de carboxylate de *tert*-butyl 4-[(3,3-diphénylpropyl)amino]-1-pipéridine (470 mg, 1,2 mmol) dans 5 ml de dichlorométhane est ajouté 246 mg (1,32 mmol) d'isocyanate de 3-(trifluorométhyl)phényle. La solution est agitée

alors ajoutés et le mélange agité pendant 30 minutes. La phase organique est lavée avec une solution saturée de bicarbonate de sodium, de chlorure de sodium, séchée sur sulfate de magnésium, filtrée et concentrée pour donner 10 g d'un solide jaune. Ce solide est purifié par chromatographie flash sur gel de silice en éluant avec un mélange heptane/acétate d'éthyle (4/1, 3/1, 2/1 puis 1/1) puis à l'acétate d'éthyle pur. Les fractions sont concentrées sous vide pour donner 5,6 g (rdt = 57 %) d'un solide jaune pâle.

RMN ^1H (CD_3OD , 400 MHz) δ : 7,27 (m, 8H) ; 7,16 (m, 2H) ; 4 (dd, $J = 6,4$ et 14Hz, 3H) ; 2,73 (m, 2H) ; 2,55 (m, 3H) ; 2,26 (q, $J = 7,6\text{Hz}$, 2H) ; 1,78 (d, $J = 12\text{Hz}$, 2H) ; 1,45 (s, 9H) ; 1,15 (qd, $J = 4,4$ et 12,8Hz, 2H). SM/CL : $m/z = 395,2$ (M+H).

Une série de 4-aminosubstitué-1-pipéridine est préparée selon cette procédure avec les autres groupes R_1 suivants :



A2) Fonctionnalisation des pipéridines

15 A2a) Synthèses d'urées et de thiourées

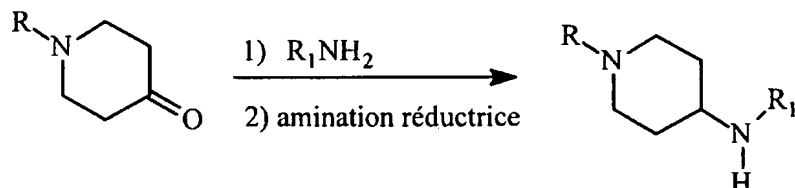
Les synthèses d'urées et de thiourées sont mises en œuvre selon la procédure décrite dans la littérature (Kaldor, S.W. ; Siegel, M.G. ; Fritz, J.E. ; Dressman, B.A. ; Hahn, P.J. *Tetrahedron Lett.* **1996**, *37*, 7193-7196 ; Kaldor, S.W. ; Fritz, J.E. ; Tang, J. ; McKinney, E.R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041-3044 ; Booth, R.J. ; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886 ; Flynn, D.L. ; Crich, J.Z. ; Devraj, R.V. ; Hockerman, S.L. ; Parlow, J.J. ; South, M.S. ; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874-4881) suivant le schéma suivant :

Les composés selon l'invention peuvent être préparés en phase solide ou liquide.

A) Synthèses en phase liquide *via* la pipéridone N-substituée

A1) Amination réductrice

Elle s'effectue selon l'étape suivante :

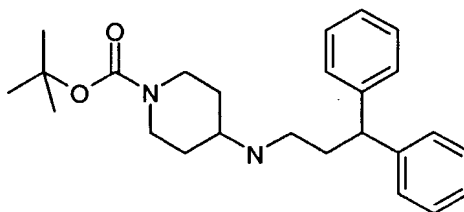


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dans laquelle R représente méthyle ou Boc et R₁ a la signification indiquée ci-dessus.

La procédure générale est la suivante : l'amination réductrice (Abdel-Magid, A.F. ; Maryanoff, C.A. ; Carson, K.G. *Tetrahedron Lett.* **1990**, *31*, 5595-5598 ; Abdel-Magid, A.F. ; Carson, K.G. ; Harris, B.D. ; Maryanoff, C.A. ; Shah, R.D., *J. Org. Chem.* **1996**, *61*, 3849-3862) de la pipéridone N-substituée est réalisée dans des solvants anhydres chlorés tel que le dichloroéthane en présence d'une amine primaire (1,1 à 1,5 éq.), d'un agent réducteur tel que le triacétoxyborohydrure de sodium (1,1 à 1,5 éq.) et d'acide acétique (10 % en masse relatif à la pipéridone N-substituée). Le mélange réactionnel est agité pendant 1 à 4 heures à température ambiante. Dans certains cas, une solution de soude (0.1 M) est ajoutée et le mélange agité pendant 20 à 90 minutes. Sinon, le mélange réactionnel est lavé avec une solution saturée de bicarbonate de sodium, chlorure de sodium, séché sur sulfate de magnésium, filtré et concentré. Le produit désiré est purifié par chromatographie flash sur gel de silice.

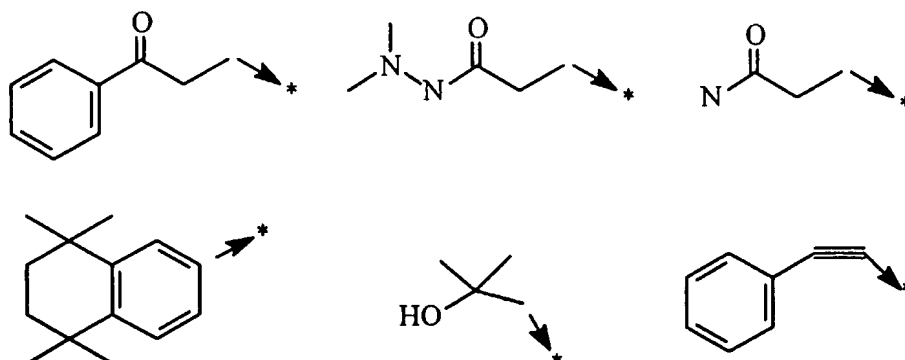
20 **Préparation 1** : Carboxylate de *tert*-butyl 4-[(3,3-diphénylpropyl)amino]-1-pipéridine (C₂₅H₃₄N₂O₂, M = 394,56)



A 5 g (25 mmol) de N-Boc-pipéridone dans 100 ml de dichloroéthane sec est ajouté la 3,3-diphénylpropylamine (5,8 g, 27,5 mmol), le triacétoxyborohydrure de sodium (6,36 g, 30 mmol) et 0,5 ml d'acide acétique. La solution jaune trouble est agitée à température ambiante pendant 1 heure. 50 ml d'une solution de soude (0.1 M) sont

25

ou bien X_2 représente un radical de formule



X_3 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, le radical vinyle substitué par un radical phényle, CF_3 , ou $-(CH_2)_pZ_{25}$ dans lequel

- 5 Z_{25} représente un radical phényle, naphthyle, thiényl, pyrazolyle ou thiazolyle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, $-NH-C(O)-$ alkyle, mono- et di-alkylamino ;

- De manière très préférentielle, R_1 représente le radical $-(CH_2)_mZ_{12}$ dans lequel $m = 2$
 10 et Z_{12} représente *bis*-phényle ou bien le radical indolyle substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux alkyle et alkoxy.

De manière très préférentielle, R_2 représente les radicaux de formule $-C(Y)NHX_1$ et $-C(O)X_2$ dans laquelle

Y représente S ;

- 15 X_1 représente un radical phényle éventuellement substitué par un ou plusieurs radicaux azido,

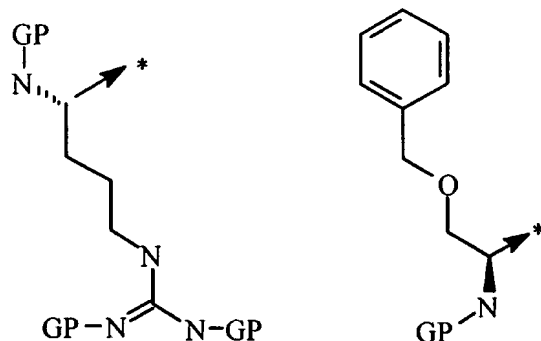
X_2 représente $-(CH_2)_pZ_{24}$ dans lequel

p est égal à 1, 2 ou 3,

- 20 Z_{24} représente cyclohexyle, ou phényle ou benzothiényl éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo ou $-CF_3$.

De manière très préférentielle, R_3 représente l'atome d'hydrogène ou le radical méthyle.

ou bien X_2 représente



X_3 représente un radical $-(CH_2)_pZ_{25}$ dans lequel Z_{25} représente le radical phényle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3 ,

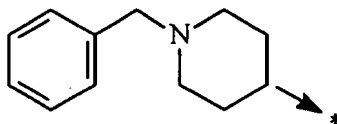
De manière préférentielle, R_3 représente l'atome d'hydrogène, un radical alkyle, alkényle ou furyl-méthyl substitué par un ou plusieurs radicaux nitro, ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(CH_2)_pZ_{22}$ dans lequel
 Z_{22} représente le radical phényle ou naphthyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, phénoxy,

X_2 représente le radical vinyle substitué par un radical phényle lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_p-U-Z_{24}$ dans lequel

Z_{24} représente alkyle, cyclohexyle, tétrahydrofuryle, bis-phényle, amino, mono ou di-alkylamino, ou phényle, indolyle, thiényl, pyridinyle, benzothiényl et furyl éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, amino, mono- et di-alkylamino, nitro, hydroxy, pyrrolyl

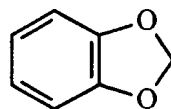
ou bien R_1 représente un radical de formule ci-dessous :



De manière préférentielle, R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

5 X_1 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexyle, cyclohexényle, *bis*-phényle, morpholino, pipéridino, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou phényle, naphthyle ou furyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, 10 alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, pipéridinosulfonyl, $-C(O)-O$ -alkyle, $-C(O)$ -alkyle ou phényle, ou bien Z_{22} représente un radical de formule



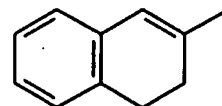
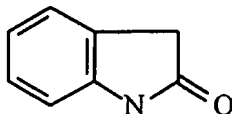
15 X_2 représente un radical alkyle, alkynyle, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_pZ_{24}$ dans lequel

W représente SO_2 ;

Z_{23} représente le radical phényle ;

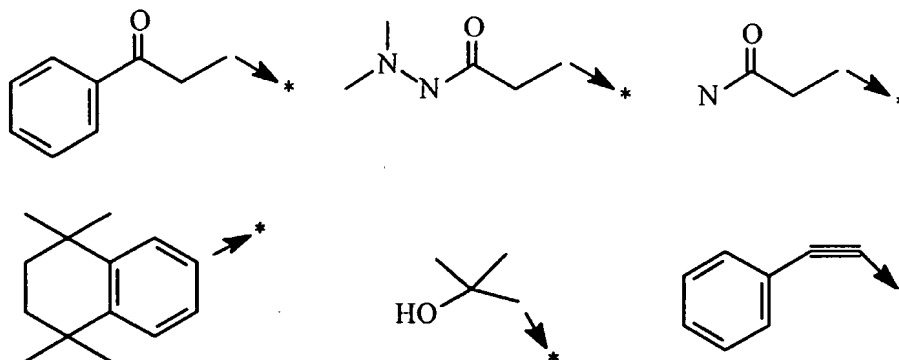
Z_{24} représente cyclohexényle, *bis*-phényle, cyclohexyle éventuellement substitué par un radical aminoalkyle, ou phényle, naphthyle, 20 benzothiényl, thiényl ou indolyle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-CF_3$, $-OCF_3$, SCF_3 , hydroxy, $-O-C(O)$ -alkyle, $-NH-C(O)$ -alkyle, mono- ou di-alkylamino, amino, ou

Z_{24} représente un radical de formule



- 12 -

ou bien X_2 représente un radical de formule



X_3 représente un radical (C_1 - C_{10})alkyle linéaire ou ramifié, le radical vinyle substitué par un radical (le radical phényle étant lui-même éventuellement substitué), CF_3 , ou $-(CH_2)_pZ_{25}$ dans lequel

5

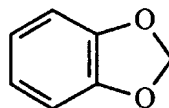
Z_{25} représente aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, $-NH-C(O)$ -alkyle, mono- et di-alkylamino.

- 10 De manière préférentielle, R_1 représente un radical (C_1 - C_6)alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

Z_{11} représente un (C_1 - C_6)alkyle,

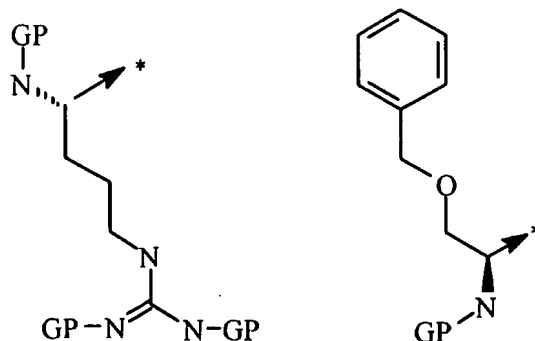
- 15 Z_{12} représente naphthyle, morpholino, *bis*-phényle, pyrrolidinyle substitué par le radical oxy, ou bien les radicaux phényle, pipérazinyle, pyridinyle et indolyle qui sont éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux bromo, fluoro, chloro, alkyle, alkoxy, $-CF_3$, $-OCF_3$;

ou bien Z_{12} représente



- 20 Y représente l'atome d'oxygène,

ou bien X_2 représente



X_3 représente un radical $-(CH_2)_p Z_{25}$ dans lequel Z_{25} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux identiques ou différents
5 choisis parmi alkoxy et CF_3 ,

R_3 représente l'atome d'hydrogène, un radical alkyle, alkenyle, hétéroarylalkyle éventuellement substitué ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(CH_2)_p Z_{22}$ dans lequel
10 Z_{22} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, phénoxy ;

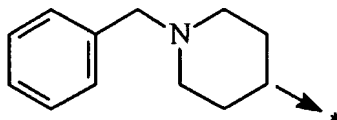
X_2 représente le radical vinyle substitué par un phényle, le radical phényle étant lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou
15 $-(CH_2)_p-U-Z_{24}$ dans lequel

Z_{24} représente alkyle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, bis-phényle, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, hydroxy, CF_3 , nitro, amino, mono- et
20 di-alkylamino, pyrrolyle,

- 10 -

Y représente l'atome d'oxygène,

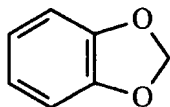
ou bien R_1 représente un radical de formule



R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

5 X_1 représente un radical (C_1-C_{15}) alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, pipéridinosulfonyl, $-C(O)-O$ -alkyle, $-C(O)$ -alkyle, ou phényle, ou bien Z_{22} représente un radical de formule



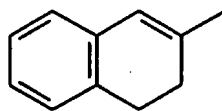
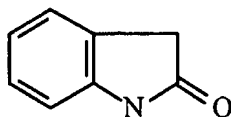
15 X_2 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, alkynyle, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_p-U-Z_{24}$ dans lequel

W représente SO_2 ,

U représente une liaison covalente,

Z_{23} représente un radical aryle ;

20 Z_{24} représente cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle éventuellement substitué par un radical aminoalkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-CF_3$, $-OCF_3$, SCF_3 , hydroxy, $-O-C(O)$ -alkyle, mono- ou di-alkylamino, amino ou Z_{24} représente un radical de formule



25

également butoxy linéaire, secondaire ou tertiaire, pentyloxy. Le terme alkylthio inférieur désigne de préférence les radicaux dans lesquels le radical alkyle est tel que défini ci-dessus comme par exemple méthylthio, éthylthio. Le terme alkylsulfonyl désigne de préférence les radicaux dans lesquels le radical alkyle est tel que défini ci-dessus.

L'expression aryle représente un radical aromatique, constitué d'un cycle ou de cycles condensés, comme par exemple le radical phényle ou naphthyle. L'expression hétéroaryle désigne un radical aromatique, constitué d'un cycle ou de cycles condensés, avec au moins un cycle contenant un ou plusieurs hétéroatomes identiques ou différents choisis parmi le soufre, l'azote ou l'oxygène. Comme exemple de radical hétéroaryle, on peut citer les radicaux thiényl, furyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, oxazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, quinoxalinyl, benzothiényl, benzofuryl, indolyl, benzoxadiazolyl.

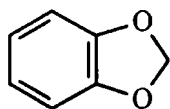
Les termes mono- et di-alkylamino désignent de préférence les radicaux dans lesquels les radicaux alkyle sont tels que définis ci-dessus, comme par exemple méthylamino, éthylamino, diméthylamino, diéthylamino ou (méthyl)(éthyl)amino.

Le symbole $\rightarrow *$ correspond au point de rattachement du radical. Lorsque le site de rattachement n'est pas précisé sur le radical, cela signifie que le rattachement s'effectue sur un des sites disponibles de ce radical pour un tel rattachement.

La présente invention a plus particulièrement pour objet des composés de formule générale I telle que définie ci-dessus dans laquelle :

R_1 représente un radical (C_1-C_6) alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

Z_{11} représente un (C_1-C_6) alkyle,
 Z_{12} représente *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle éventuellement substitué, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy,
ou bien Z_{12} représente



vii) le ou les substituant(s) que peut porter le radical aralkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , OCF_3 , $OCHF_2$, SCF_3 , $SCHF_2$, nitro, cyano, $-C(O)O$ -alkyle, alkylsulfonyl, thiadiazolyle, ou bien les radicaux phényle et phénoxy dont le radical phényle est éventuellement substitué par un ou plusieurs radicaux halo.

viii) le ou les substituant(s) que peut porter le radical hétéroarylalkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo ou nitro.

Dans les définitions indiquées ci-dessus, l'expression halo représente le radical fluoro, chloro, bromo ou iodo, de préférence chloro, fluoro ou bromo. L'expression alkyle (lorsqu'il n'est pas donné plus de précision), représente de préférence un radical alkyle ayant de 1 à 6 atomes de carbone, linéaire ou ramifié, tels que les radicaux méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, *sec*-butyle et *tert*-butyle, pentyle ou amyle, isopentyle, neopentyle, hexyle ou isohexyle. Parmi les radicaux alkyle contenant de 1 à 15 atomes de carbone, on peut citer les alkyles tels que définis ci-dessus mais également les radicaux heptyle, octyle, nonyle, décyle, dodécyle, tridécyle ou pentadécyle.

Par alkényle, lorsqu'il n'est pas donné plus de précision, on entend un radical alkyle linéaire ou ramifié comptant de 1 à 6 atomes de carbone et présentant au moins une insaturation (double liaison), comme par exemple vinyle, allyle, propényle, butényle ou pentényle. Par alkynyle, lorsqu'il n'est pas donné plus de précision, on entend un radical alkyle linéaire ou ramifié comptant de 1 à 6 atomes de carbone et présentant au moins une double insaturation (triple liaison) comme par exemple un radical éthyne, propargyle, butynyle ou pentynyle.

Le terme cycloalkyle désigne un système monocyclique carboné comprenant de 3 à 7 atomes de carbone, et de préférence les cycles cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexyle. L'expression hétérocycloalkyle désigne un cycloalkyle saturé contenant de 2 à 7 atomes de carbones et au moins un hétéroatome. Ce radical peut contenir plusieurs hétéroatomes identiques ou différents. De préférence, les hétéroatomes sont choisis parmi l'oxygène, le soufre ou l'azote. Comme exemples d'hétérocycloalkyle, on peut citer le cycle pyrrolidine, pyrrolidinone, imidazolidine, pyrrazolidine, isothiazolidine, thiazolidine, isoxazolidine, pipéridine, pipérazine ou morpholine.

Les radicaux alkoxy peuvent correspondre aux radicaux alkyle indiqués ci-dessus comme par exemple les radicaux méthoxy, éthoxy, propyloxy ou isopropyloxy mais

ou leurs sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables, à l'exclusion des composés de formule générale I dans laquelle avec R_1 représente le radical alkyle, alkényle ou benzyle, R_2 benzyloxy éventuellement substitué et R_3 aralkyle.

5 L'invention a plus particulièrement pour objet les produits de formule générale I telle que définie ci-dessus, caractérisée en ce que

i) le ou les substituant(s) que peuvent porter les radicaux aryle que représentent Z_{11} et Z_{12} et hétéroaryle que représente Z_{12} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phényle, phénoxy, aminosulfonyle ;

10 ii) le ou les substituant(s) que peut porter le radical hétérocycloalkyle que représente Z_{12} sont choisis indépendamment parmi les radicaux oxy et alkyle ;

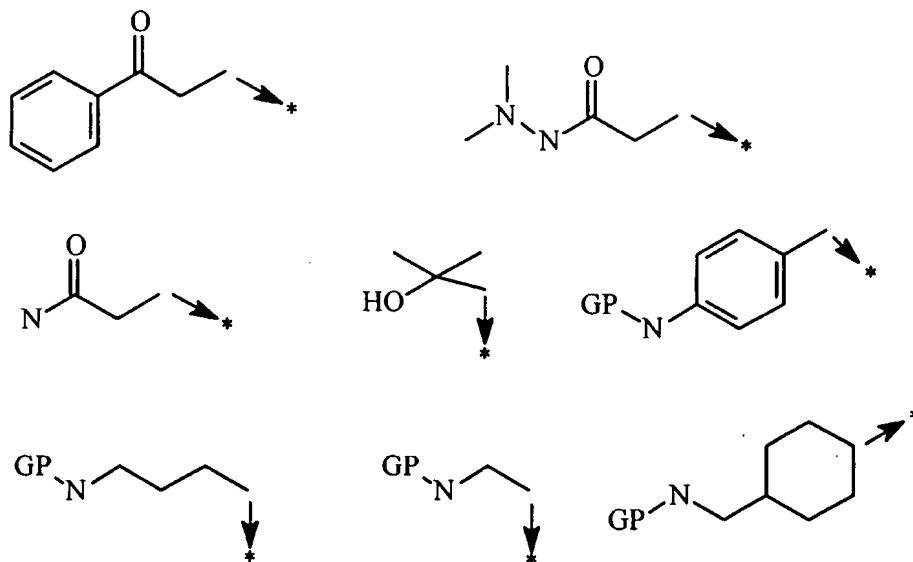
iii) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{22} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkényle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, aminosulfonyle, pipéridinosulfonyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, $-C(O)$ -alkyle, ou phényle, phénoxy, phénylthio, benzyloxy, le radical phényle pouvant être substitué ;

20 iv) le ou les substituant(s) que peut porter les radicaux aryle que représentent Z_{23} et Z_{24} , cycloalkyle et hétéroaryle que représente Z_{24} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , $OCHF_2$, SCF_3 , nitro, cyano, azido, hydroxy, $-C(O)O$ -alkyle, $-O-C(O)$ -alkyle, $-NH-C(O)$ -alkyle, alkylsulfonyle, mono- ou di-alkylamino, amino, aminoalkyle, pyrrolyle, pyrrolydinyne ou bien les radicaux phényle, phénoxy, phénylthio, benzyle, benzyloxy dont le radical aryle est éventuellement substitué par un ou plusieurs radicaux alkyle, CF_3 ou halo ;

25 v) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{25} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , OCF_3 , nitro, cyano, $-NH-C(O)$ -alkyle, alkylsulfonyle, amino, mono- et di-alkylamino, phényle, pyridino ;

30 vi) le substituant que peut porter le radical alkyle que représente R_3 est le radical cyano.

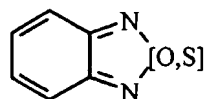
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où le groupe protecteur (GP) représente H ou le *tert*-butyloxycarbonyle ;

X_3 représente un radical (C_1 - C_{10})alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), CF_3 , ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente aryle ou hétéroaryle éventuellement substitué,
ou bien X_3 représente un radical de formule



éventuellement substitué par un ou plusieurs radicaux halo

identiques ou différents ;

Y représente un atome d'oxygène ou de soufre ;

10 W représente un atome d'oxygène, de soufre ou SO_2 ;

U représente une liaison covalente ou l'atome d'oxygène ;

n est un entier de 0 à 4 ;

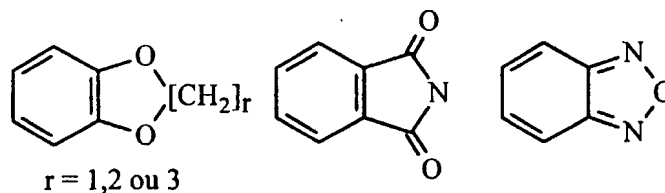
m est un entier de 1 à 6 ;

p est un entier de 0 à 6 ;

15 q est un entier de 0 à 2,

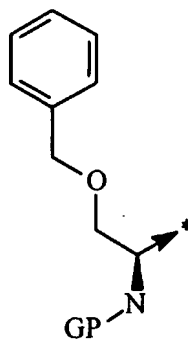
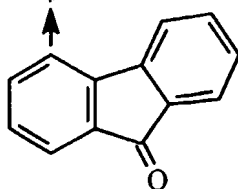
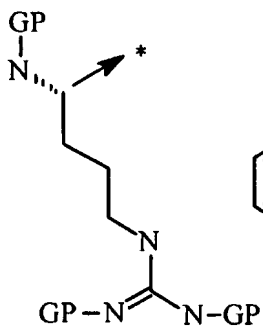
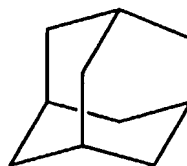
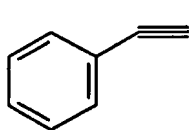
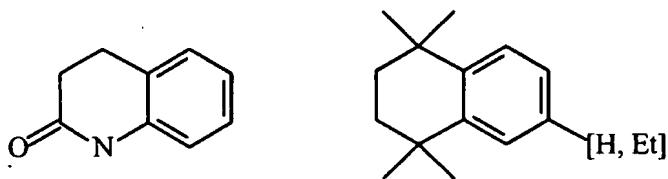
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Z_{24} représente alkyle, cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle éventuellement substitué, (C_3-C_7) hétérocycloalkyle, cyano, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué, ou Z_{24} représente un radical de formule



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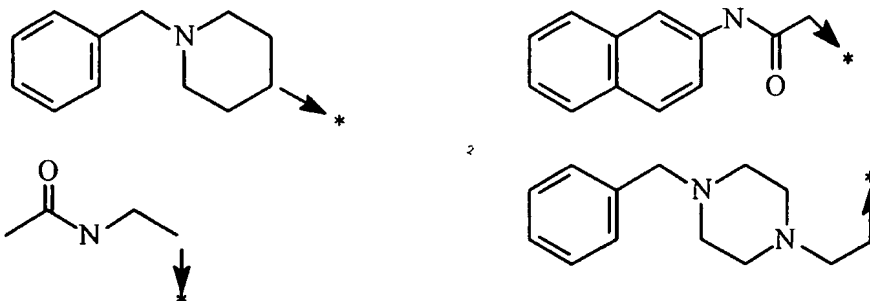
ou bien X_2 représente un radical représenté ci-dessous :



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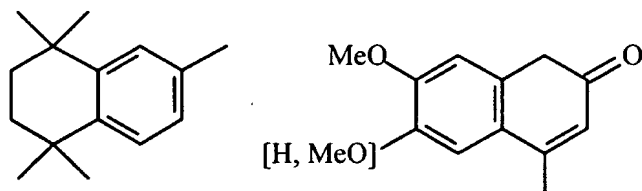
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ou bien R_1 représente un radical de formule



R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 ;

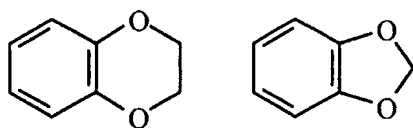
R_3 représente l'atome d'hydrogène, un radical alkyle éventuellement substitué, alkényle, alkynyle, aralkyle éventuellement substitué, hétéroarylalkyle éventuellement substitué, ou un radical de formule $-C(Y)-NHX_1$, $-(CH_2)_n-C(O)X_2$, SO_2X_3 ou



X_1 représente un radical (C_1-C_{15}) alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m-Y-Z_{21}$ ou $-(CH_2)_pZ_{22}$ dans lequel

10 Z_{21} représente un (C_1-C_6) alkyle

Z_{22} représente cyclohexényle, indanyle, bis-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou aryle ou hétéroaryle éventuellement substitué, ou Z_{22} représente un radical de formule



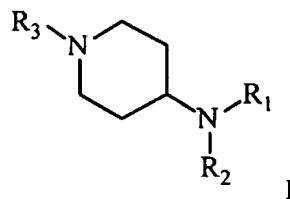
15 X_2 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), alkynyle, ou un radical de formule $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_p-U-Z_{24}$ dans lequel

Z_{23} représente un (C_1-C_6) alkyle ou aryle éventuellement substitué ;

maladie polykystique des ovaires, les pseudokystes pancréatiques et ascites, la leucémie, le méningiome, la cachexie cancéreuse, l'inhibition des H pylori, le psoriasis ainsi que la maladie d'Alzheimer. On peut également citer l'ostéoporose.

Les déposants ont trouvé que les composés de formule générale décrits ci-après
 5 présentaient une affinité et une sélectivité pour les récepteurs de la somatostatine. Comme la somatostatine et ses analogues peptidiques ont souvent une mauvaise biodisponibilité par voie orale et une faible sélectivité (Robinson, C., *Drugs of the Future*, 1994, 19, 992; Reubi, J.C. et al., *TIPS*, 1995, 16, 110), lesdits composés, agonistes ou antagonistes non-peptidiques de la somatostatine, peuvent être
 10 avantageusement utilisés pour traiter les états pathologiques ou les maladies tels que présentés ci-dessus et dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s). De manière préférentielle, lesdits composés peuvent être utilisés pour le traitement de l'acromégalie, des adénomes hypophysaires ou des tumeurs gastroentéropancréatiques endocriniennes dont le
 15 syndrome carcinoïde.

La présente invention a donc pour objet des composés de formule générale



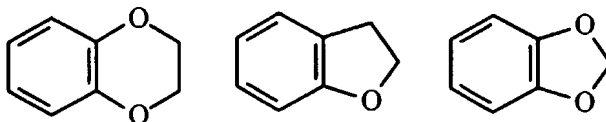
sous forme racémique, d'énantiomère ou toutes combinaisons de ces formes, dans laquelle :

R_1 représente un radical (C_1-C_{16}) alkyle linéaire ou ramifié, alkényle, alkynyle,
 20 $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

Z_{11} représente un (C_1-C_6) alkyle ou aryle éventuellement substitué,

Z_{12} représente cyano, cyclohexényle, bis-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle éventuellement substitué, aryle éventuellement substitué ou hétéroaryle éventuellement substitué,

25 ou bien Z_{12} représente un radical de formule



tumeurs gastrointestinales sécrétrices ; le traitement du cancer comme les hépatomes ; l'inhibition de l'angiogénèse, le traitement des désordres inflammatoires comme l'arthrite ; le rejet chronique des allogreffes ; l'angioplastie ; la prévention des saignements des vaisseaux greffés et des saignements gastrointestinaux. Les
5 agonistes de la somatostatine peuvent aussi être utilisés pour diminuer le poids d'un patient.

Parmi les désordres pathologiques associés à la somatostatine (Moreau J.P. et al., *Life Sciences*, 1987, **40**, 419 ; Harris A.G. et al., *The European Journal of Medicine*, 1993, **2**, 97-105), on peut donc citer par exemple : l'acromégalie, les adénomes
10 hypophysaires, la maladie de Cushing, les gonadotrophinomes et les prolactinomes, les effets secondaires cataboliques des glucocorticoïdes, le diabète insulino-dépendant, la rétinopathie diabétique, la néphropathie diabétique, l'hyperthyroïdie, le gigantisme, les tumeurs gastroentéro-pancréatiques endocriniennes dont le syndrome carcinoïde, le VIPome, l'insulinome, la
15 nésidioblastose, l'hyperinsulinémie, le glucagonome, le gastrinome et le syndrome de Zollinger-Ellison, le GRFome ainsi que le saignement aigu des varices œsophagiennes, le reflux gastroœsophagien, le reflux gastroduodénal, la pancréatite, les fistules entérocutanées et pancréatiques mais aussi les diarrhées, les diarrhées réfractaires du syndrome d'immunodépression acquise, la diarrhée chronique
20 sécrétoire, la diarrhée associée avec le syndrome de l'intestin irrité, les troubles liés au peptide libérateur de gastrine, les pathologies secondaires aux greffes intestinales, l'hypertension portale ainsi que les hémorragies des varices chez des malades avec cirrhose, l'hémorragie gastro-intestinale, l'hémorragie de l'ulcère gastroduodénal, la maladie de Crohn, les scléroses systémiques, le dumping syndrome, le syndrome du petit intestin, l'hypotension, la sclérodermie et le carcinome thyroïdien médullaire, les maladies liées à l'hyperprolifération cellulaire comme les cancers et plus particulièrement le cancer du sein, le cancer de la prostate, le cancer thyroïdien ainsi
25 que le cancer pancréatique et le cancer colorectal, les fibroses et plus particulièrement la fibrose du rein, la fibrose du foie, la fibrose du poumon, la fibrose de la peau, également la fibrose du système nerveux central ainsi que celle du nez et la fibrose induite par la chimiothérapie, et d'autres domaines thérapeutiques comme, par exemple, les céphalées y compris les céphalées associées aux tumeurs hypophysaires, les douleurs, les accès de panique, la chimiothérapie, la cicatrisation des plaies, l'insuffisance rénale résultant d'un retard de croissance, l'obésité et retard
30 de croissance lié à l'obésité, le retard de croissance utérin, la dysplasie du squelette, le syndrome de Noonan, le syndrome d'apnée du sommeil, la maladie de Graves, la

Dérivés de 4-aminopipéridine et leur utilisation en tant que médicament

La présente demande a pour objet de nouveaux dérivés de 4-aminopipéridines et leurs procédés de préparation par des méthodes de synthèse en parallèle en phase liquide et solide. Ces produits ayant une bonne affinité avec certains sous-types de récepteurs de la somatostatine, ils sont particulièrement intéressants pour traiter les
5 états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s).

La somatostatine (SST) est un tétradécapeptide cyclique qui a été isolé pour la première fois de l'hypothalamus en tant que substance inhibitrice de l'hormone de croissance (Brazeau P. et al., *Science* 1973, **179**, 77-79). Elle intervient également en
10 tant que neurotransmetteur dans le cerveau (Reisine T. et al., *Neuroscience* 1995, **67**, 777-790 ; Reisine et al., *Endocrinology* 1995, **16**, 427-442). Le clonage moléculaire a permis de montrer que la bioactivité de la somatostatine dépend directement d'une famille de cinq récepteurs liés à la membrane.

L'hétérogénéité des fonctions biologiques de la somatostatine a conduit à des études
15 pour essayer d'identifier les relations structure-activité des analogues peptidiques sur les récepteurs de la somatostatine, ce qui a amené la découverte de 5 sous-types de récepteurs (Yamada et al., *Proc. Natl. Acad. Sci. U.S.A.*, **89**, 251-255, 1992 ; Raynor, K. et al, *Mol. Pharmacol.*, **44**, 385-392, 1993). Les rôles fonctionnels de ces récepteurs sont actuellement activement étudiés. Les affinités avec les différents
20 sous-types de récepteurs de la somatostatine ont été associés au traitement des désordres / maladies suivants. L'activation des sous-types 2 et 5 a été associée à la suppression de l'hormone de croissance (GH) et plus particulièrement à celle des adénomes sécrétant GH (acromégalie) et de ceux sécrétant l'hormone TSH. L'activation du sous-type 2 mais pas du sous-type 5 a été associée au traitement des
25 adénomes sécrétant la prolactine. D'autres indications associées avec l'activation des sous-types de récepteurs de la somatostatine sont la resténose, l'inhibition de la sécrétion d'insuline et/ou de glucagon et en particulier le diabète mellitus, l'hyperlipidémie, l'insensibilité à l'insuline, le Syndrome X, l'angiopathie, la rétinopathie proliférative, le phénomène de Dawn et la néphropathie ; l'inhibition de
30 la sécrétion d'acide gastrique et en particulier les ulcères peptiques, les fistules entérocutanées et pancréaticocutanées, le syndrome du colon irritable, le syndrome de Dumping, le syndrome des diarrhées aqueuses, les diarrhées reliées au SIDA, les diarrhées induites par la chimiothérapie, la pancréatite aiguë ou chronique et les

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(81) États désignés (national): AE, AG, AI, AM, AT, AU, AZ,
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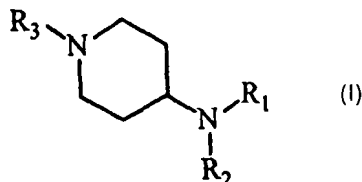
— Avec rapport de recherche internationale.
— Avant l'expiration du délai prévu pour la modification des
revendications, sera republiée si des modifications sont
reçues.

En ce qui concerne les codes à deux lettres et autres abrégia-
tions, se référer aux "Notes explicatives relatives aux codes et
abréviations" figurant au début de chaque numéro ordinaire de
la Gazette du PCT.

(54) Title: 4-AMINOPIPERIDINE DERIVATIVES AND THEIR USE AS MEDICINE

(54) Titre: DERIVES DE 4-AMINOPIPERIDINE ET LEUR UTILISATION EN TANT QUE MEDICAMENT

WO 01/44191 A1



(57) Abstract: The invention concerns novel 4-aminopiperidine derivatives of formula (I) wherein: R₁, R₂ and R₃ represent various variable groups, their preparation methods by parallel synthesis processes in liquid and solid phase. Said products have good affinity with certain sub-types of somatostatin receptors, and they are particularly useful for treating pathological conditions or diseases wherein one (or several) somatostatin receptor(s) is/are involved.

(57) Abrégé: La présente demande a pour objet de nouveaux dérivés de 4-aminopipéridines de formule (I) dans laquelle R₁, R₂ et R₃ représentent divers groupes variables, leurs procédés de préparation par des méthodes de synthèse en parallèle en phase liquide et solide. Ces produits ayant une bonne affinité avec certains sous-types de récepteurs de la somatostatine, ils sont particulièrement intéressants pour traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s).

IDS REFERENCES



FOR

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/08/00

International application No.

PCT/DK 00/00264

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9901423	A1	14/01/99	AU	7908398 A	25/01/99
				EP	0994848 A	26/04/00
				NO	996550 A	29/02/00
				ZA	9805759 A	25/01/99

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				DK	346278 A	07/02/79
				ES	472384 A	01/10/79
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				ES	479933 A	01/12/79
				IL	55242 D	00/00/00
				IT	1106623 B	11/11/85
				IT	7850601 D	00/00/00
				JP	54041881 A	03/04/79
ZA	7804463 A	25/07/79				

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00264

*Claims 87-88 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv).

Nevertheless, a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compound(s)/composition(s).

**Present claims 1-58 and 69-88 relate to an extremely large number of possible compounds. In fact, the claims contains so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, a limited search has been carried out on the basis of claims 59-68.

Claim 5 (when A = -NR⁷-CH₂-) and claim 9 (A = -NH-CH₂-) do not seem to be depending on claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00264

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **87-88**
because they relate to subject matter not required to be searched by this Authority, namely:
See extra sheet*
2. ☒ Claims Nos.: **1-58, 69-88**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See extra sheet**
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00264

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 237/32, C07C 243/24, C07C 271/40, C07C 275/28, C07D 209/48,
C07D 257/04, C07D 333/04, A61K 31/15, A61K 31/165, A61K31/17, A61K 31/33,
According to International Patent Classification (IPC) or to both national classification and IPC A61P 3/04, A61P 3/10

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9901423 A1 (NOVO NORDISK A/S ET AL), 14 January 1999 (14.01.99) --	1-88
A	EP 0847992 A1 (MITSUI CHEMICALS, INC.), 17 June 1998 (17.06.98) --	1-88
A	EP 0000816 A1 (BEECHAM GROUP LIMITED), 21 February 1979 (21.02.79) -- -----	1-88

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 Sept 2000

Date of mailing of the international search report

27-09-2000

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

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Authorized officer

Nebil Gecer/ELY

Telephone No. +46 8 782 25 00

81. Use according to claim 80 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.
82. Use according to claim 80 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.
83. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.
84. Use according to any one of the claims 75 to 83 in a regimen which additionally comprises treatment with another antidiabetic agent.
85. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of obesity.
86. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of obesity in a regimen which additionally comprises treatment with another antiobesity agent.
87. A method for the treatment and/or prevention of disorders or diseases mediated by a glucagon antagonistic action, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 71 or a pharmaceutical composition according to claim 73 or 74.
88. The method according to claim 87, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

71. A compound according to any one of the preceding claims, which is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, IGT, Type 2 diabetes, Type 1 diabetes and obesity.

5 72. A compound according to any one of the claims 1 to 71 for use as a medicament.

73. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 71 together with one or more pharmaceutically acceptable carriers or excipients.

10

74. A pharmaceutical composition according to claim 73 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 71.

15

75. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

20

76. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.

25

77. Use of a compound according to any one of the claims 1 to 71 for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

78. Use of a compound according to any one of the claims 1 to 71 for the manufacture of a medicament for lowering blood glucose in a mammal.

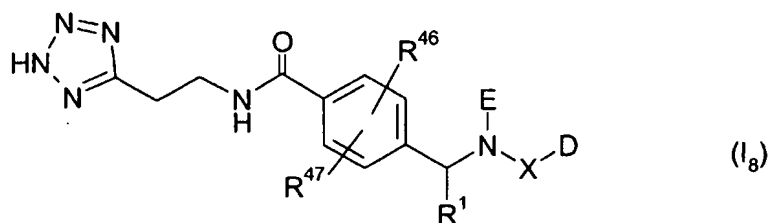
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79. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of IGT.

80. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.

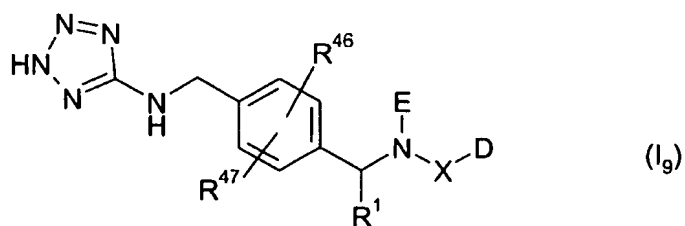
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66. A compound according to claim 1 of the general formula (I₈):



5 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

67. A compound according to claim 1 of the general formula (I₉):



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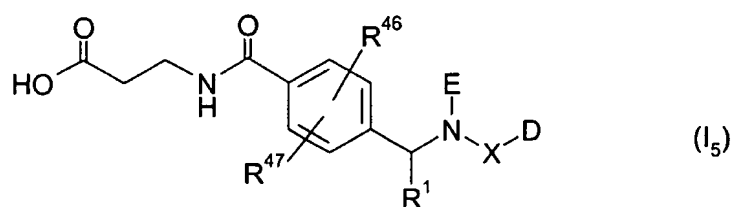
wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

15 68. A compound according to anyone of the claims 59 to 61 or 63 to 67, wherein R⁴⁶ and R⁴⁷ are both hydrogen.

69. A compound according to any one of the preceding claims, which has an IC₅₀ value of no greater than 5 μM as determined by the Glucagon Binding Assay (I), Glucagon Binding
 20 Assay (II) or Glucagon Binding Assay (III) disclosed herein.

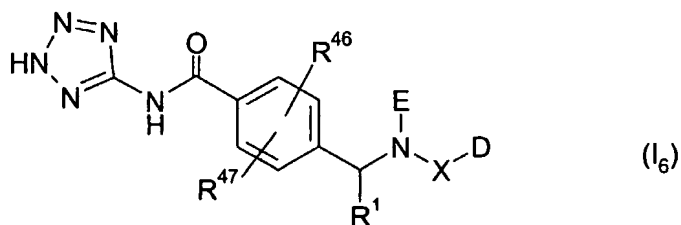
70. A compound according to claim 69 characterized by having a glucagon antagonistic activity as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein corresponding to an IC₅₀ value of less than 1 μM,
 25 preferably of less than 500 nM and even more preferred of less than 100 nM.

63. A compound according to claim 1 of the general formula (I₅):



5 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

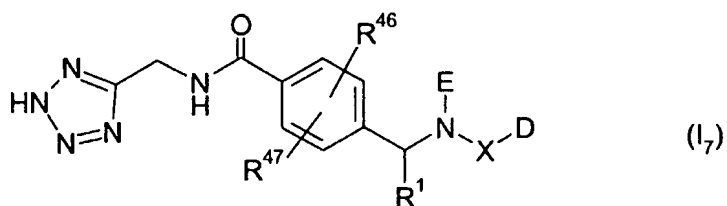
64. A compound according to claim 1 of the general formula (I₆):



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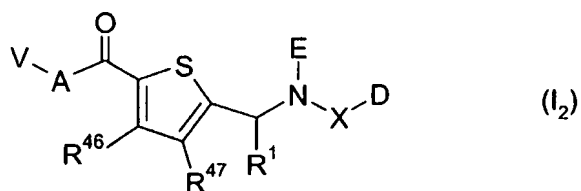
wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

15 65. A compound according to claim 1 of the general formula (I₇):



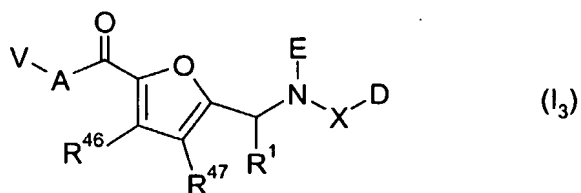
20 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

60. A compound according to claim 1 of the general formula (I₂):



5 wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

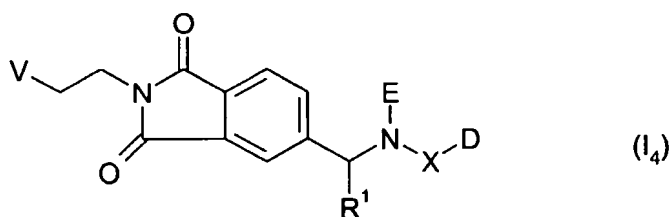
61. A compound according to claim 1 of the general formula (I₃):



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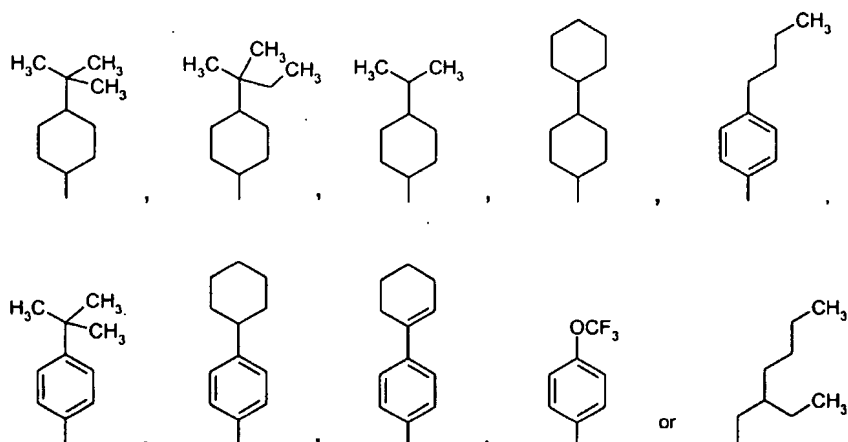
wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

15 62. A compound according to claim 1 of the general formula (I₄):

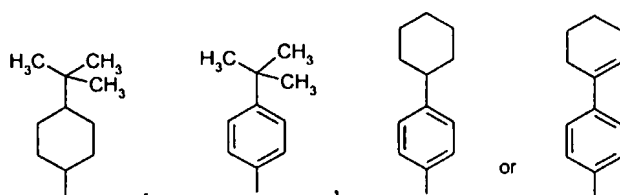


20 wherein V is -C(O)OR², -C(O)NR²R³ or -C(O)NR²OR³, and R¹, R², R³, E, X and D are as defined in claim 1 or in any one of the preceding claims.

57. A compound according to claim 46, wherein E is

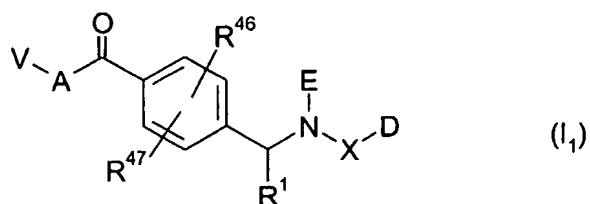


5 58. A compound according to claim 57, wherein E is



59. A compound according to claim 1 of the general formula (I₁):

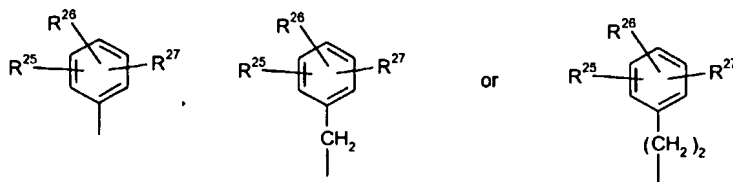
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wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

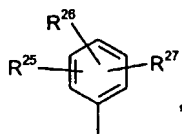
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53. A compound according to claim 46, wherein E is



5 wherein R^{25} , R^{26} and R^{27} are as defined in claim 1.

54. A compound according to claim 53, wherein E is

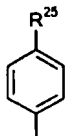


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wherein R^{25} , R^{26} and R^{27} are as defined in claim 1.

55. A compound according to claim 53 or 54, wherein R^{25} , R^{26} and R^{27} independently are selected from hydrogen, halogen, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-8} -cycloalkyl, C_{4-8} -cycloalkenyl, $-CF_3$,
 15 $-OCF_3$ or $-NR^{42}R^{43}$, wherein R^{42} and R^{43} are as defined in claim 1.

56. A compound according to claim 55, wherein E is

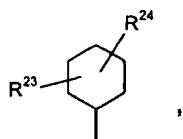


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wherein R^{25} is $-OCF_3$, $-CF_3$, C_{1-6} -alkyl such as *tert*-butyl, piperidyl, C_{3-8} -cycloalkyl such as cyclohexyl or C_{4-8} -cycloalkenyl such as cyclohexenyl.

48. A compound according to claim 47, wherein R^{34} and R^{35} are both C_{1-6} -alkyl.

49. A compound according to claim 45, wherein E is

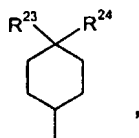


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wherein R^{23} and R^{24} are as defined in claim 1.

50. A compound according to claim 49, wherein E is

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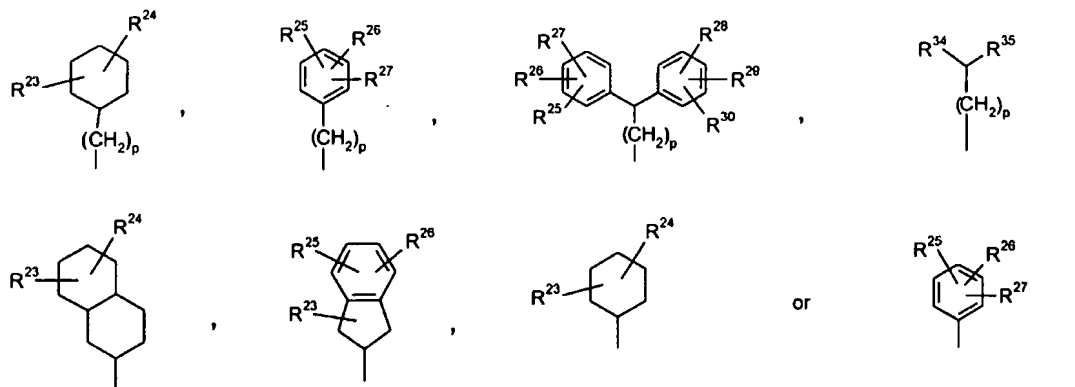
wherein R^{23} and R^{24} are as defined in claim 1.

15 51. A compound according to claim 49 or 50, wherein R^{23} and R^{24} independently are selected from hydrogen, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkylidene, phenoxy, phenyl, $-C(O)NR^{36}R^{37}$ and $-OC(O)NH$ -phenyl, of which the phenyl moiety optionally may be substituted with $-OCF_3$, wherein R^{36} and R^{37} are as defined in claim 1, or R^{23} and R^{24} together form the radical $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-$, $-O-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-O-$, $-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$,
20 wherein t , l , R^{40} and R^{41} are as defined in claim 1.

52. A compound according to claim 51, wherein R^{23} is hydrogen and R^{24} is C_{1-6} -alkyl such as *tert*-butyl or C_{3-8} -cycloalkyl such as cyclohexyl, wherein R^{23} and R^{24} are both C_{1-6} -alkyl or wherein R^{23} and R^{24} together form the radical $-(CH_2)_5-$.

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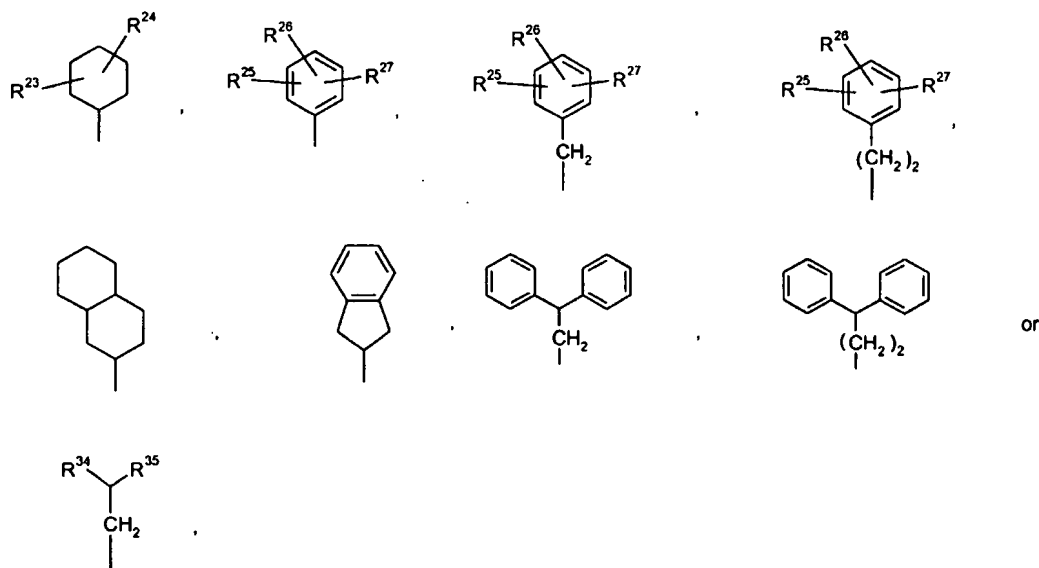
45. A compound according to claim 44, wherein E is



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wherein p, R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³⁴ and R³⁵ are as defined in claim 1.

46. A compound according to claim 45, wherein E is



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wherein R²³, R²⁴, R²⁵, R²⁶, R²⁷, R³⁴ and R³⁵ are as defined in claim 1.

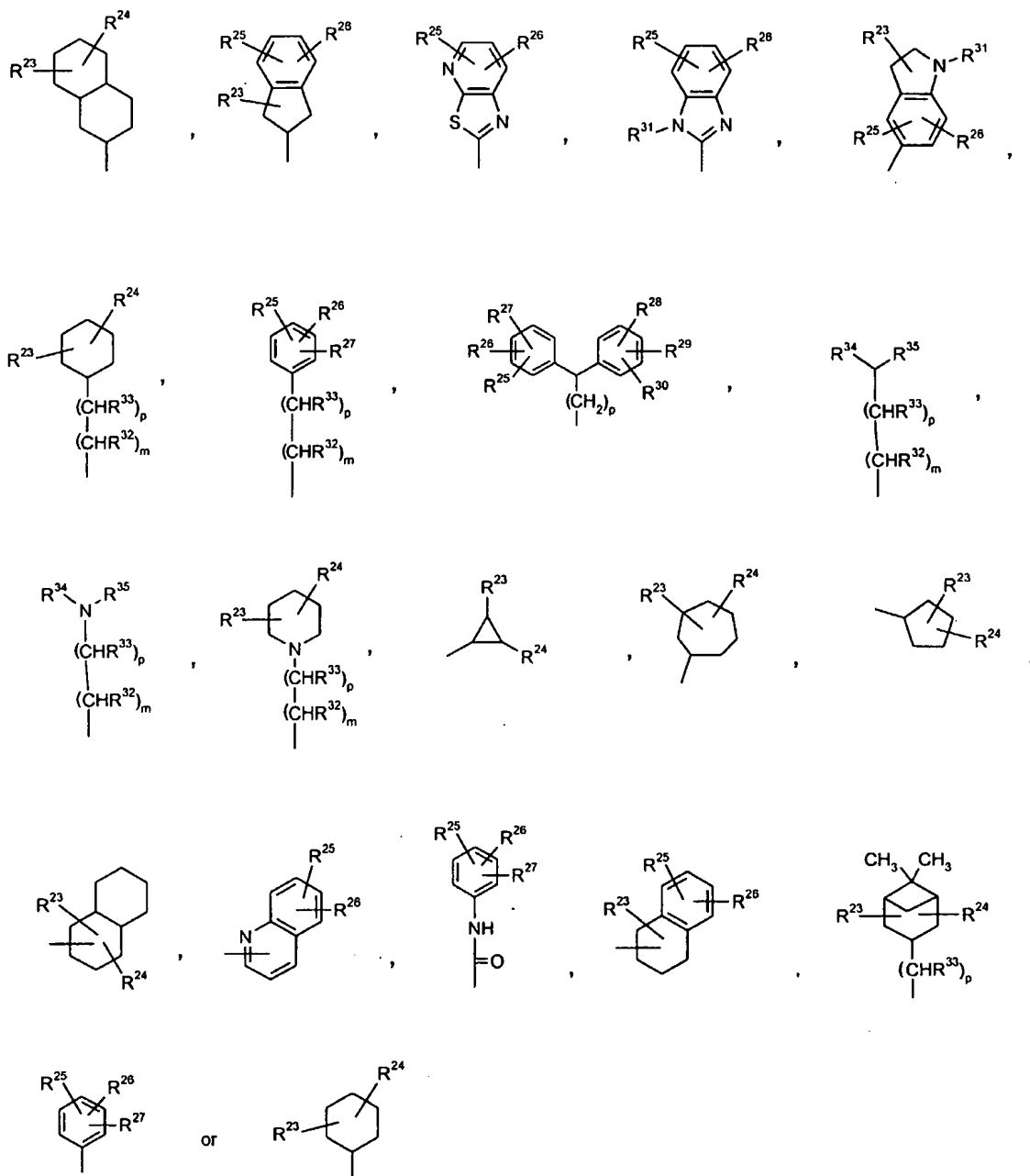
47. A compound according to claim 46, wherein R³⁴ and R³⁵ independently are C₁₋₆-alkyl, hydrogen or C₁₋₆-alkoxy.

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wherein

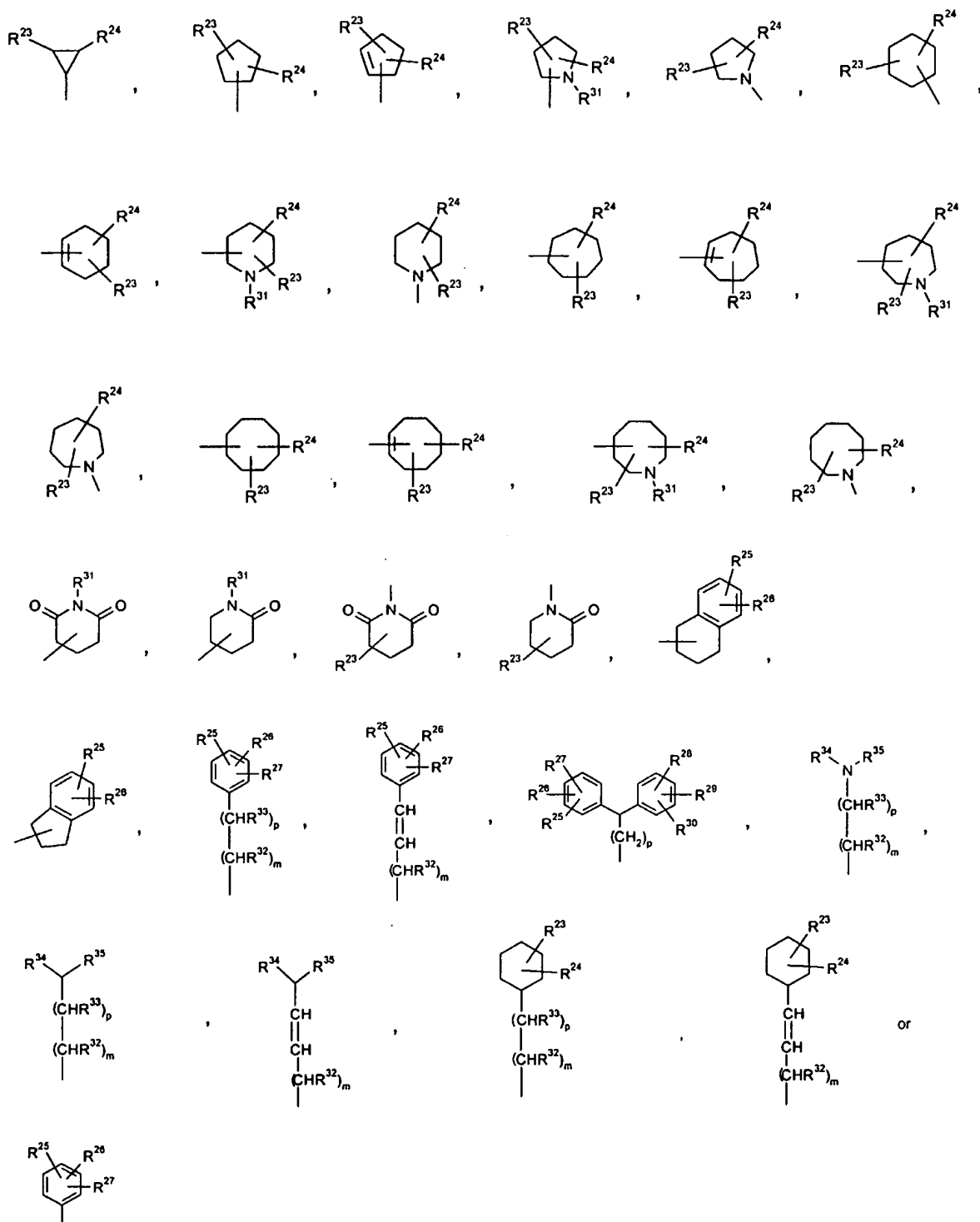
m, p and R^{23} to R^{35} are as defined in claim 1.

5 44. A compound according to claim 43, wherein E is



wherein m, p and R^{23} to R^{35} are as defined in claim 1.

43. A compound according to any one of the preceding claims, wherein E is



40. A compound according to claim 30, wherein R^{16} is hydrogen, R^{17} is $-OCF_3$ and R^{18} is $-S(O)_2CH_3$, $-CH_2O$ -tri- C_{1-6} -alkylsilyl, benzoxazolyl or $-CH_2OH$.
41. A compound according to claim 30, wherein R^{16} is hydrogen, R^{17} is C_{1-6} -alkyl and R^{18} is
5 $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.
42. A compound according to claim 30, wherein R^{16} , R^{17} and R^{18} are selected from hydrogen, $-OCF_3$, $-CF_3$, $-Br$, $-F$ and $-Cl$.

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, $-C(O)OR^{21}$ or C_{1-6} -alkyl, wherein R^{21} is hydrogen or C_{1-6} -alkyl, or

5

wherein R^{16} and R^{17} in adjacent positions form the radical $-CF_2-O-CF_2-O-$ or $-O-CF_2-CF_2-O-$, and R^{18} is hydrogen.

33. A compound according to claim 32, wherein R^{16} , R^{17} and R^{18} independently are hydrogen, halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6} -alkyl, C_{1-6} -alkoxy, $-S-C_{1-6}$ -alkyl, $-C(O)OC_{1-6}$ -alkyl, $-S(O)_2C_{1-6}$ -alkyl, $-S(O)_2CF_3$, $-C(O)N(C_{1-6}-alkyl)(C_{1-6}-alkyl)$, $-S(O)_2N(phenyl)(C_{1-6}-alkyl)$, $-C(=O)C_{1-6}$ -alkyl, $-CH_2OH$, $-CH_2O(tri-C_{1-6}-alkylsilyl)$, 2,3-dihydroindol-1-ylsulfonyl, phenoxy, phenyl, 4-chlorophenyl, 1,3,5-trimethylbenzyl, benzoxazolyl, 2-methyltetrazol-5-yl, 2-methyl-3-methoxycarbonylfuran-5-yl or 3-isopropyl-[1,2,4]oxadiazol-5-yl).

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34. A compound according to any one of the claims 30 to 33, wherein one of R^{16} to R^{18} is hydrogen.

35. A compound according to any one of the claims 30 to 33, wherein two of R^{16} to R^{18} are hydrogen.

20

36. A compound according to claim 30, wherein R^{16} and R^{17} are both hydrogen and R^{18} is $-OCF_3$, $-SCF_3$, $-CF_3$, $-S(O)_2CH_3$, phenyl, halogen, C_{1-6} -alkyl, nitro, $-S-C_{1-6}$ -alkyl or $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.

25

37. A compound according to claim 30, wherein R^{16} and R^{17} are both hydrogen and R^{18} is $-OCF_3$ or halogen.

38. A compound according to claim 30, wherein R^{16} is hydrogen and R^{17} and R^{18} are both halogen or are both $-CF_3$.

30

39. A compound according to claim 30, wherein R^{16} is hydrogen, R^{17} is $-CF_3$ and R^{18} is halogen, $-CN$, C_{1-6} -alkoxy or $-OCF_3$.

35

phenoxy, phenoxycarbonyl, phenyl, phenyl-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -CN, -CF₃, -OCF₃, -NO₂, -C(O)OR²¹, -OR²¹, -NR²¹R²² or C₁₋₆-alkyl, wherein R²¹ and
5 R²² independently are hydrogen or C₁₋₆-alkyl, or

wherein R¹⁶ and R¹⁷ in adjacent positions form the radical -O-CH₂-O-, -CF₂-O-CF₂-O- or -O-CF₂-CF₂-O-, and R¹⁸ is hydrogen.

10 31. A compound according to claim 30, wherein R¹⁶, R¹⁷ and R¹⁸ independently are

hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, -SCF₃, C₁₋₆-alkyl, C₁₋₆-alkyl substituted with hydroxy, C₁₋₆-alkyl substituted with -S(O)₂R²¹, C₁₋₆-alkoxy, -S-C₁₋₆-alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C₃₋₈-cyclo-
15 alkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio or C₃₋₈-cycloalkylthio,

wherein R²¹ and R²² independently are hydrogen, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, phenyl or 2,3-dihydroindolyl, or R²¹ and R²² together with the nitrogen atom to which they are attached form a piperidine ring,
20

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -C(O)OR²¹ or C₁₋₆-alkyl, wherein R²¹ is hydrogen or C₁₋₆-alkyl, or

25 wherein R¹⁶ and R¹⁷ in adjacent positions form the radical -CF₂-O-CF₂-O- or -O-CF₂-CF₂-O-, and R¹⁸ is hydrogen.

32. A compound according to claim 31, wherein R¹⁶, R¹⁷ and R¹⁸ independently are

30 hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, -SCF₃, C₁₋₆-alkyl, C₁₋₆-alkyl substituted with hydroxy, C₁₋₆-alkoxy, -S-C₁₋₆-alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)₂R²¹, -(O)₂CF₃ or -S(O)₂NR²¹R²²,

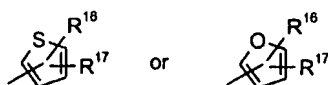
wherein R²¹ and R²² independently are hydrogen, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, phenyl or
35 2,3-dihydroindolyl,

25. A compound according to claim 24, wherein R^{16} and R^{17} are both hydrogen and R^{20} is C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl.

5 26. A compound according to claim 24 or 25, wherein R^{20} is cyclopropylmethyl, butyl or isopropyl.

27. A compound according to claim 26, wherein R^{20} is isopropyl.

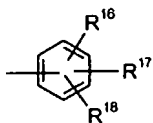
10 28. A compound according to claim 23, wherein D is



wherein R^{16} and R^{17} are as defined in claim 1.

15

29. A compound according to claim 23, wherein D is



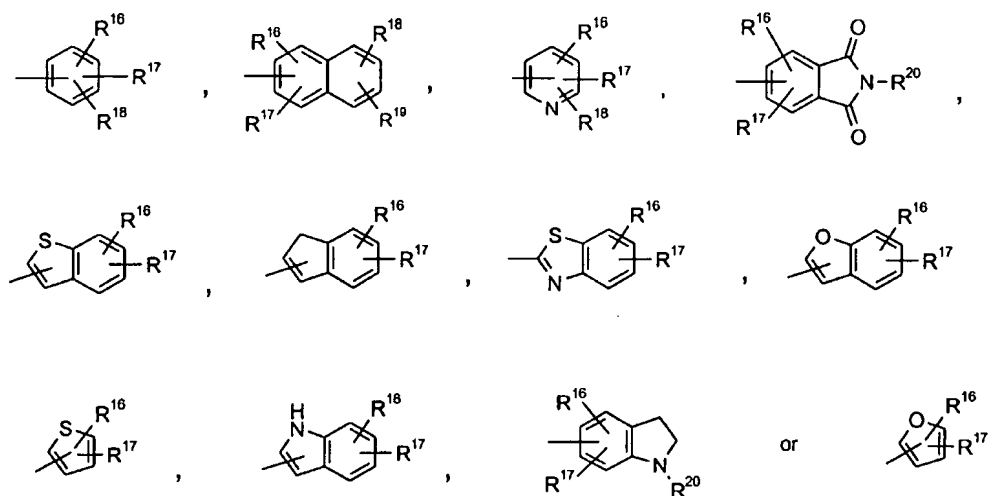
20 wherein R^{16} , R^{17} and R^{18} are as defined in claim 1.

30. A compound according to any one of the claims 22, 23, 28 or 29, wherein R^{16} , R^{17} and R^{18} independently are

25 hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, hydroxy, -SCF₃, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkyl substituted with -S(O)₂ R^{21} , C_{1-6} -alkoxy, -S- C_{1-6} -alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio or C_{3-8} -cycloalkylthio,

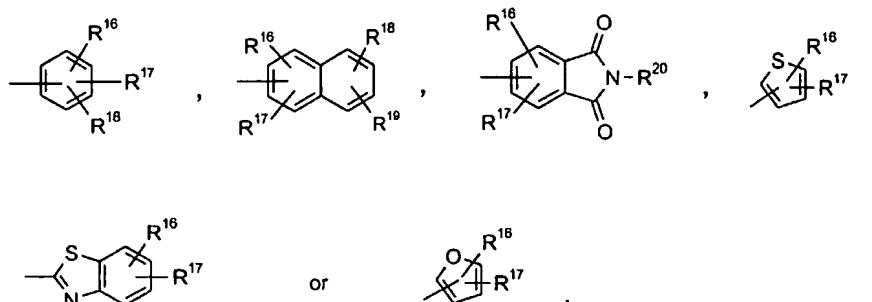
30 wherein R^{21} and R^{22} independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, phenyl, phenyl- C_{1-6} -alkyl, 2,3-dihydroindolyl or isoindolyl, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidine ring,

22. A compound according to any one of the claims 1 to 21, wherein D is



5 wherein R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²⁰ are as defined in claim 1.

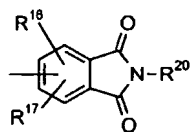
23. A compound according to claim 22, wherein D is



10

wherein R¹⁶, R¹⁷, R¹⁸ and R²⁰ are as defined in claim 1.

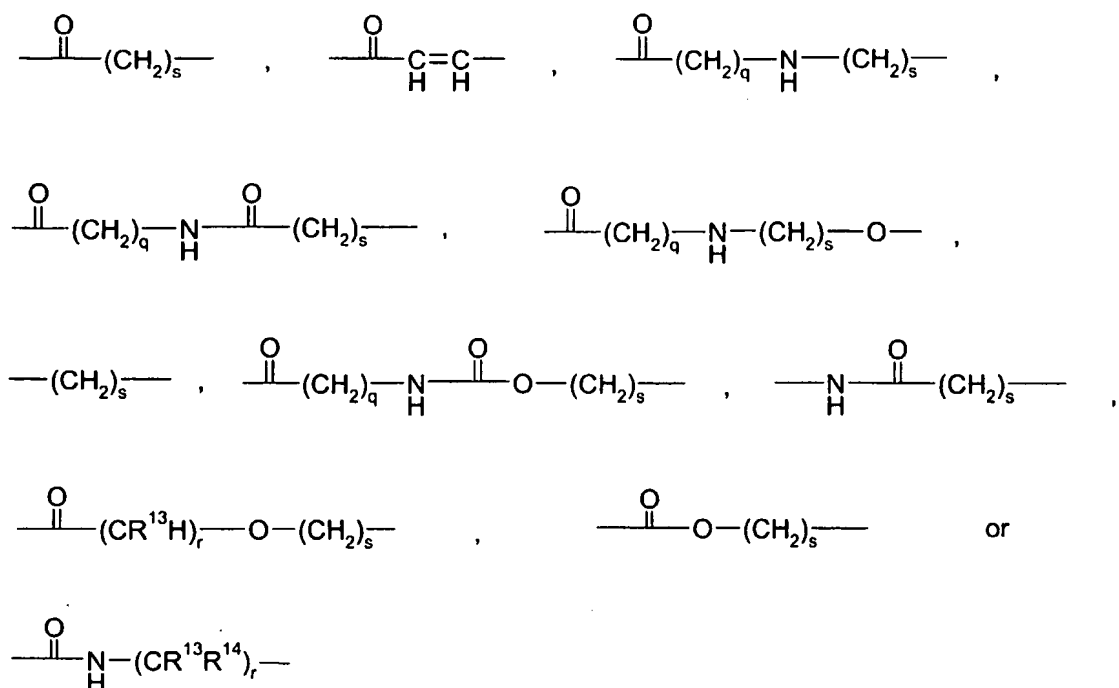
24. A compound according to claim 23, wherein D is



15

wherein R¹⁶, R¹⁷ and R²⁰ are as defined in claim 1.

17. A compound according to claim 16, wherein X is



5 wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R¹³ is hydrogen or C₁₋₆-alkyl.

18. A compound according to claim 17, wherein X is -C(O)NH-, -C(O)NHCH₂-,
-C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -C(O)CH=CH-, -(CH₂)_s-, -C(O)-, -C(O)O-
or -NHC(O)-, wherein s is 0 or 1.

10

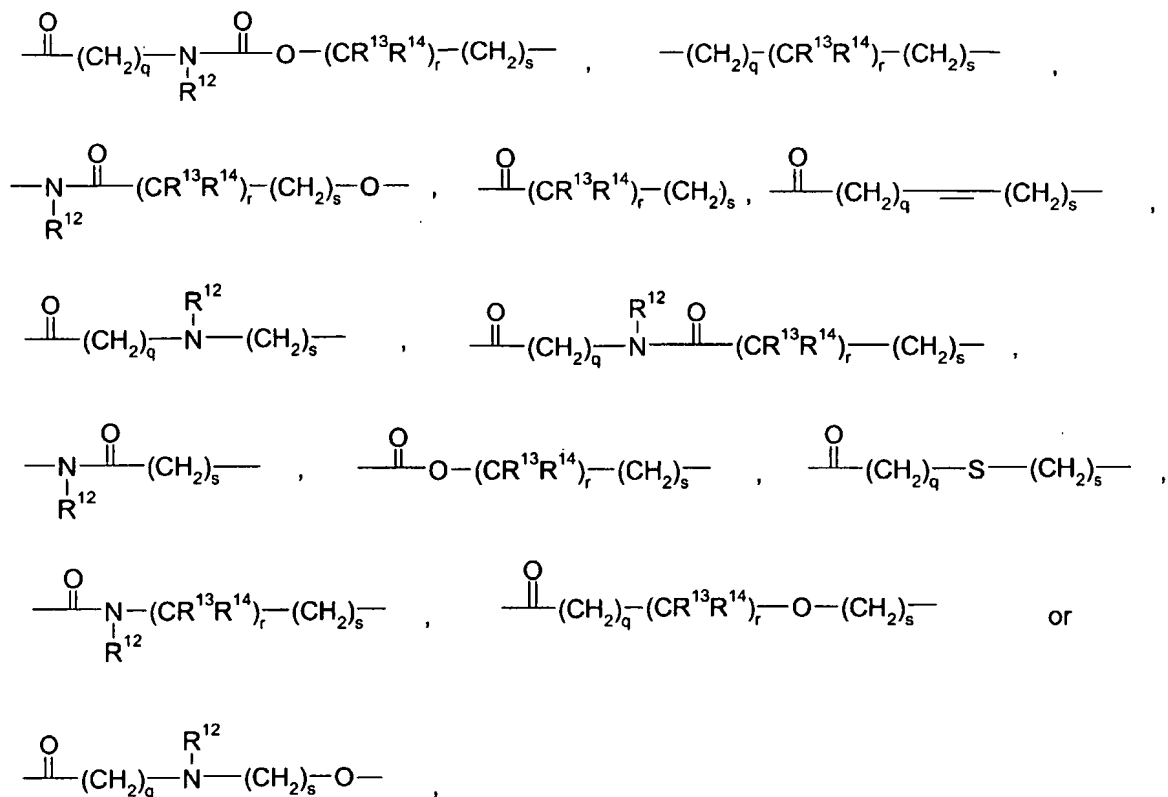
19. A compound according to claim 18, wherein X is -C(O)NH-, -C(O)NHCH₂-,
-C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -CH₂-, -C(O)- or -NHC(O)-.

20. A compound according to claim 19, wherein X is -C(O)NH-.

15

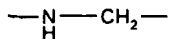
21. A compound according to claim 19, wherein X is -C(O)NHCH(CH₃)-.

16. A compound according to any one of the claims 1 to 15, wherein X is



5 wherein q, r, s, R¹², R¹³ and R¹⁴ are as defined in claim 1.

9. A compound according to claim 5, wherein A is

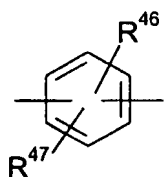


5

10. A compound according to any one of the claims 1 to 9, wherein Y is -C(O)-.

11. A compound according to any one of the claims 1 to 9, wherein Y is a valence bond.

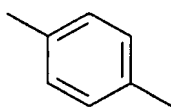
10 12. A compound according to any one of the claims 1 to 11, wherein Z is



wherein R⁴⁶ and R⁴⁷ are as defined in claim 1.

15

13. A compound according to claim 12, wherein Z is



20 14. A compound according to any one of the claims 1 to 13, wherein R¹ is hydrogen.

15. A compound according to any one of the claims 1 to 13, wherein R¹ is methyl.

R^{34} and R^{35} when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

5 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

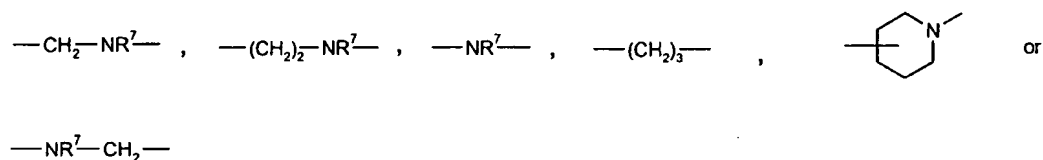
2. A compound according to claim 1, wherein V is $-C(O)OH$, $-S(O)_2OH$, $-C(O)NHOH$ or 5-tetrazolyl.

10

3. A compound according to claim 2, wherein V is $-C(O)OH$.

4. A compound according to claim 2, wherein V is 5-tetrazolyl.

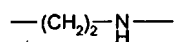
15 5. A compound according to any one of the claims 1 to 4, wherein A is



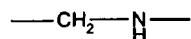
wherein R^7 is as defined in claim 1.

20

6. A compound according to claim 5, wherein A is

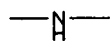


25 7. A compound according to claim 5, wherein A is



8. A compound according to claim 5, wherein A is

30





wherein

5 t and l independently are 0, 1, 2, 3, 4 or 5,

R⁴⁰ and R⁴¹ independently are hydrogen or C₁₋₆-alkyl,

10 R²⁵ to R³⁰ independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl,

wherein R⁴² and R⁴³ independently are hydrogen or C₁₋₆-alkyl, or

15 R⁴² and R⁴³ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

20 R³¹, R³² and R³³ independently are hydrogen or C₁₋₆-alkyl,

R³⁴ and R³⁵ independently are

- hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkanoyl, -C(O)NR⁴⁴R⁴⁵ or -S(O)₂R⁴⁵,
- 25 • aryl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkanoyl or aryl-C₁₋₆-alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C₁₋₆-alkyl,

30 wherein R⁴⁴ and R⁴⁵ independently are hydrogen or C₁₋₆-alkyl, or

R³⁴ and R³⁵ when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

- aryl, aryloxy, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -NR³⁶S(O)₂R³⁷, -S(O)₂NR³⁶R³⁷, -S(O)NR³⁶R³⁷, -S(O)R³⁶, -S(O)₂R³⁶, -OS(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂OR³⁶, -CH₂NR³⁶R³⁷, -OC(O)R³⁶, -C(O)R³⁶ and -C(O)OR³⁶,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

wherein R³⁶ and R³⁷ independently are hydrogen, C₁₋₆-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and C₁₋₆-alkyl,

wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_i-CR⁴⁰R⁴¹-(CH₂)_j-O-, -(CH₂)_i-CR⁴⁰R⁴¹-(CH₂)_j- or

R²³ and R²⁴ independently are

- hydrogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 5 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ or -C(O)OR³⁶,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

10 which may optionally be substituted with one or more substituents selected from
 -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

- 15 • C₃₋₈-cycloalkyl, C₃₋₈-cycloalkylidene, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-
 C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-
 C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-
 C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

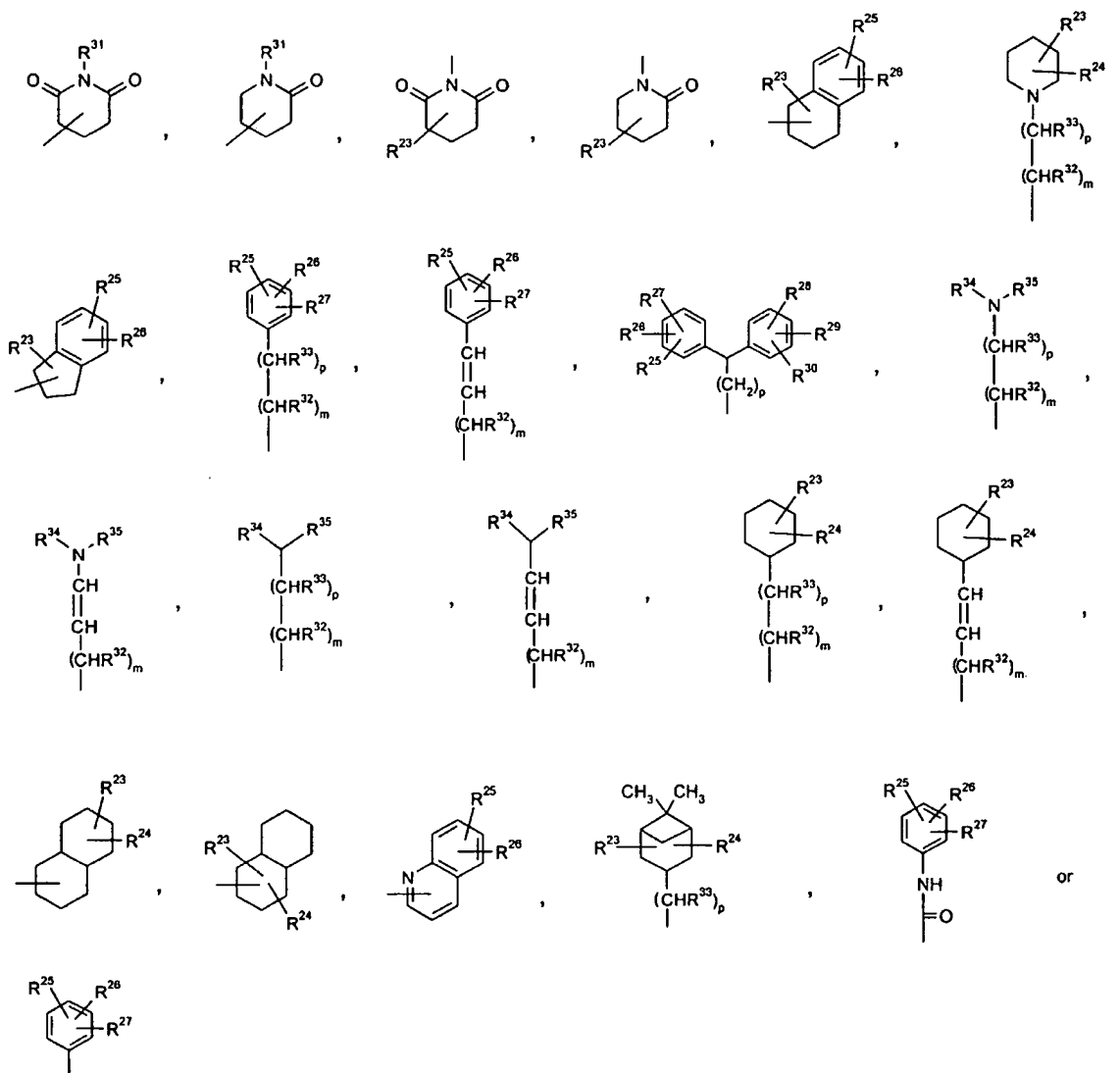
20 of which the cyclic moieties optionally may be substituted with one or more substituents selected from

- CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 25 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

30 which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷,
 -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and
 -C(O)OR³⁶,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom when present, or



wherein

10

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

5 halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
 -OC(O)R²¹, -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

10 which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

15 wherein R²¹ and R²² independently are hydrogen, -CF₃, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cycloalkyl,
 C₃₋₈-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl or heteroaryl,

or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom
 20 may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge
 -(CR^{16'}R^{17'})_a-O-(CR^{18'}R^{19'})_c-O-,

25 wherein

a is 0, 1 or 2,

30 c is 1 or 2,

R^{16'}, R^{17'}, R^{18'} and R^{19'} independently are hydrogen, C₁₋₆-alkyl or halogen,

R²⁰ and R^{20'} independently are hydrogen, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₃₋₈-cycloalkyl-C₁₋₆-
 35 alkyl,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -
 CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
 -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

- C₃₋₈-cycloalkyl, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyloxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio, C₃₋₈-cycloalkylthio, C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

-CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
 -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

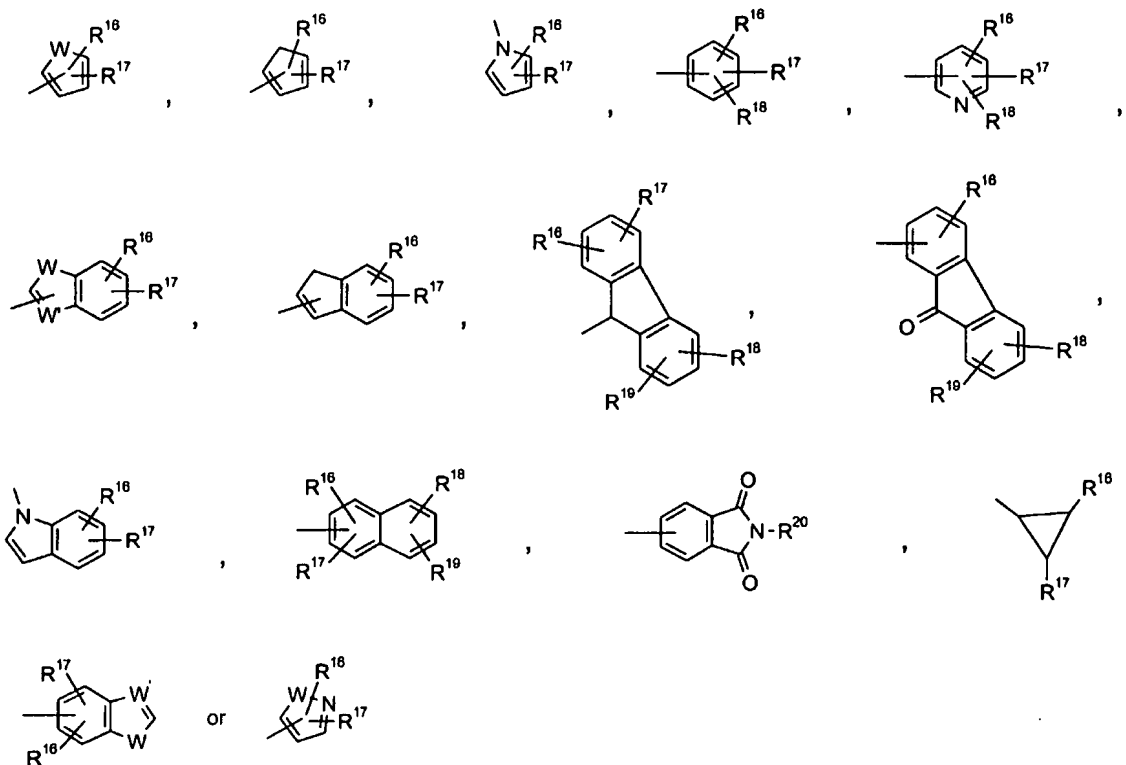
which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

R^{12} , R^{13} , R^{14} and R^{15} independently are hydrogen or C_{1-6} -alkyl,

D is



wherein

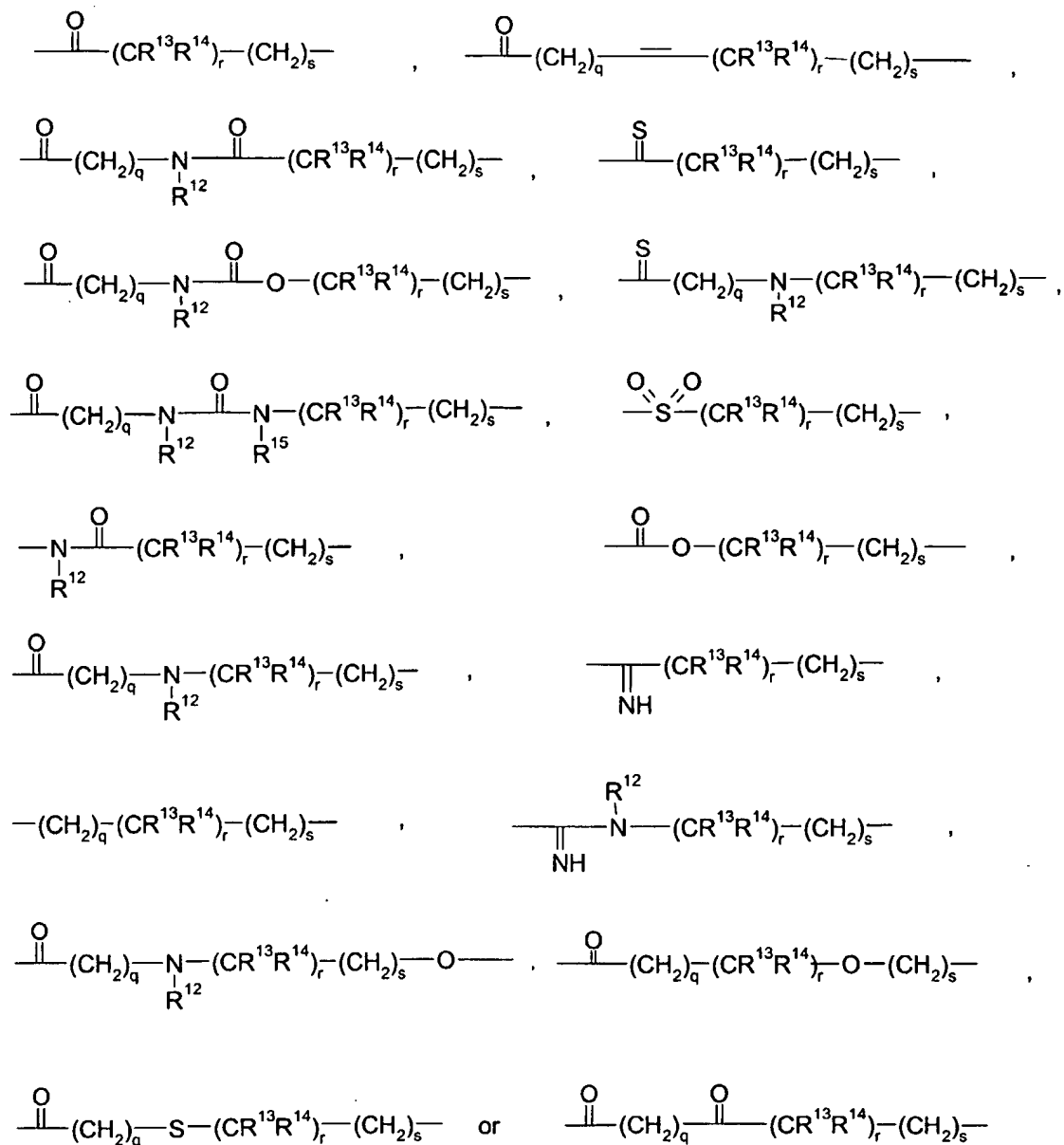
W is -O-, -S-, -S(O)₂- or -NR²⁰-,

W' is =CR²⁰- or =N-,

R^{16} , R^{17} , R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹, -C(O)R²¹ or -C(O)OR²¹,

X is



5 wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^7 is hydrogen, C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl,

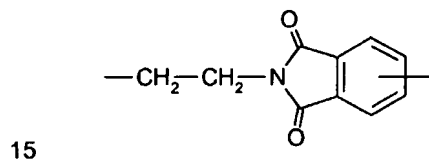
5 Y is $-C(O)-$, $-S(O)_2-$, $-O-$ or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

10 which may optionally be substituted with one or two groups R^{46} and R^{47} selected from hydrogen, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{10}$, $-NR^{10}R^{11}$ and C_{1-6} -alkyl,

wherein R^{10} and R^{11} independently are hydrogen or C_{1-6} -alkyl,

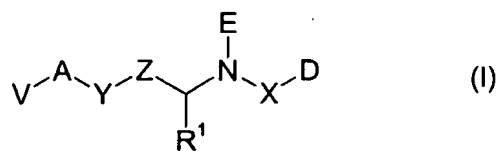
or $-A-Y-Z-$ together are



R^1 is hydrogen or C_{1-6} -alkyl,

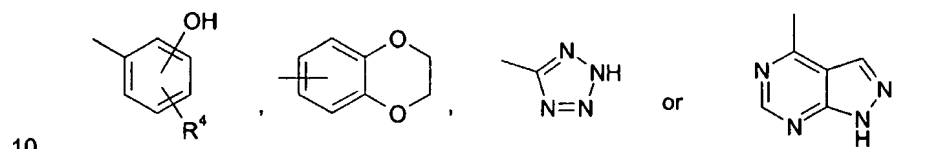
CLAIMS

1. A compound of the general formula (I):



wherein

V is $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$, $-\text{S}(\text{O})_2\text{OR}^2$,



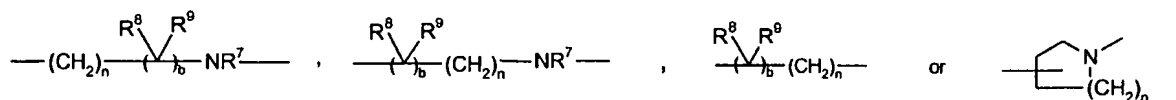
wherein

R^2 and R^3 independently are hydrogen or C_{1-6} -alkyl,

R^4 is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{OR}^5$, $-\text{NR}^5\text{R}^6$ or C_{1-6} -alkyl,

wherein R^5 and R^6 independently are hydrogen or C_{1-6} -alkyl,

20 A is



wherein

25

b is 0 or 1,

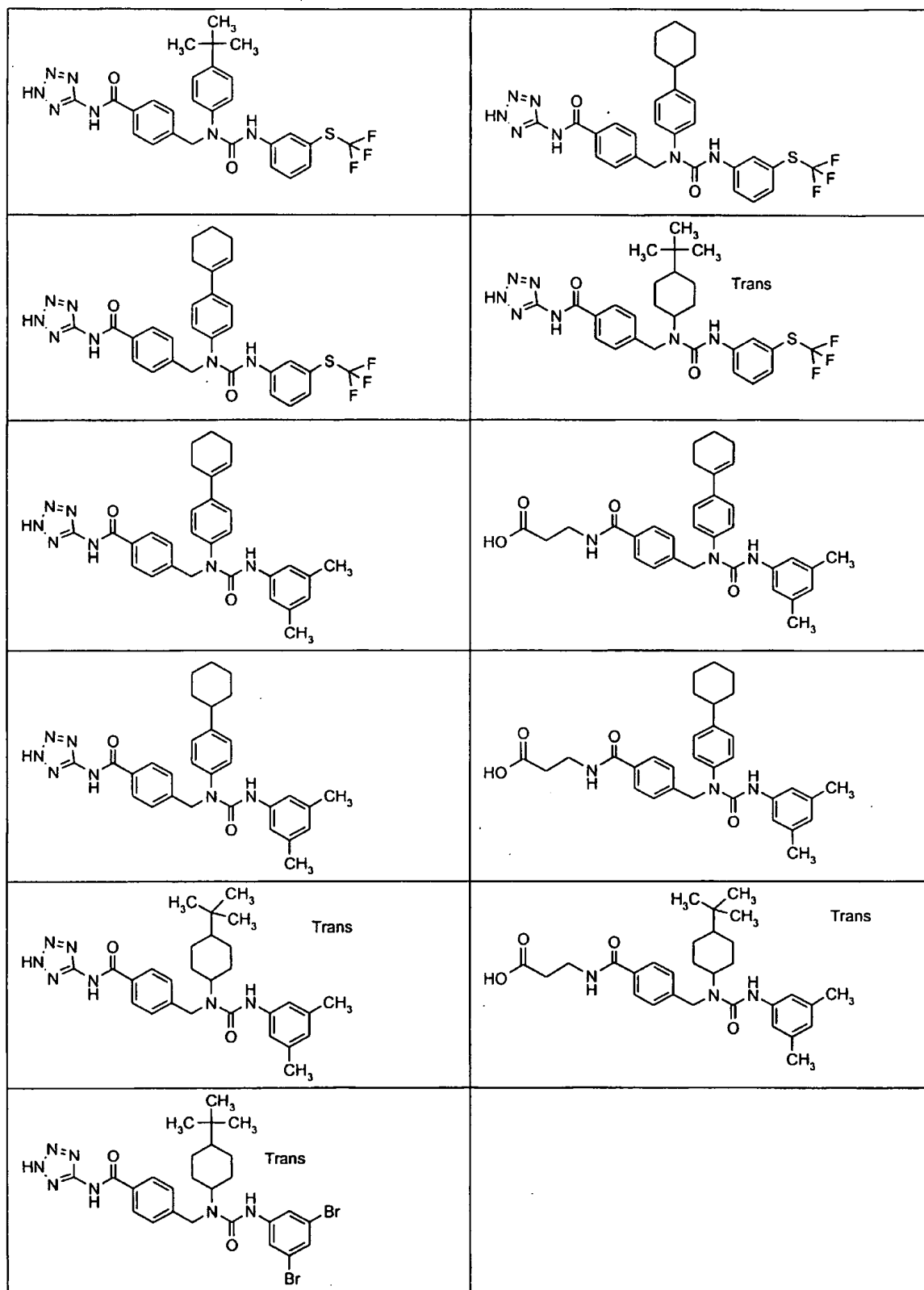
n is 0, 1, 2 or 3,

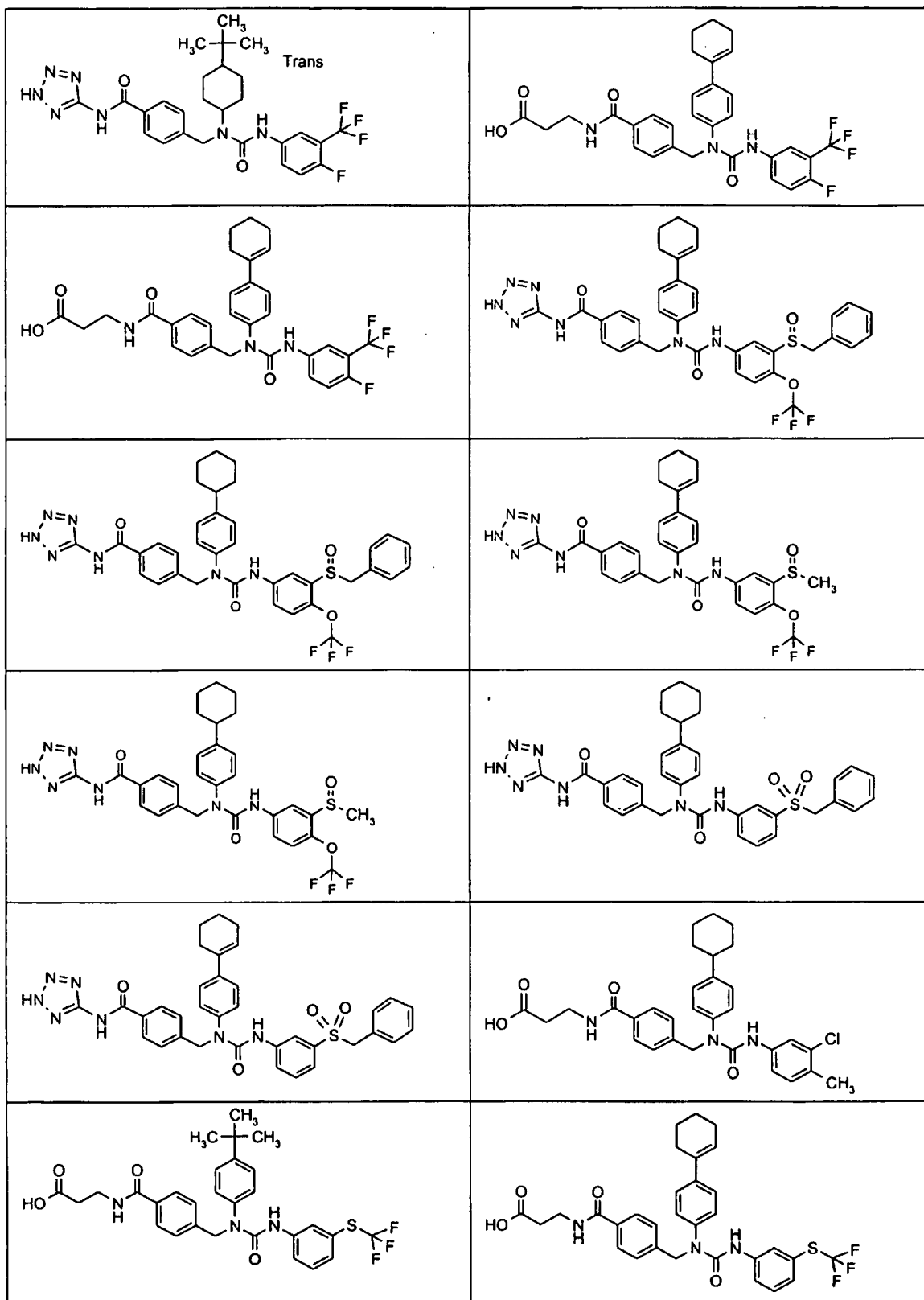
It should be apparent from the foregoing that other starting materials and other intermediate compounds can be substituted in the above procedures to prepare all of the compounds of the invention. The methods disclosed herein are based on established chemical techniques, as will be apparent to those skilled in the art, and therefore all of the compounds of the invention are

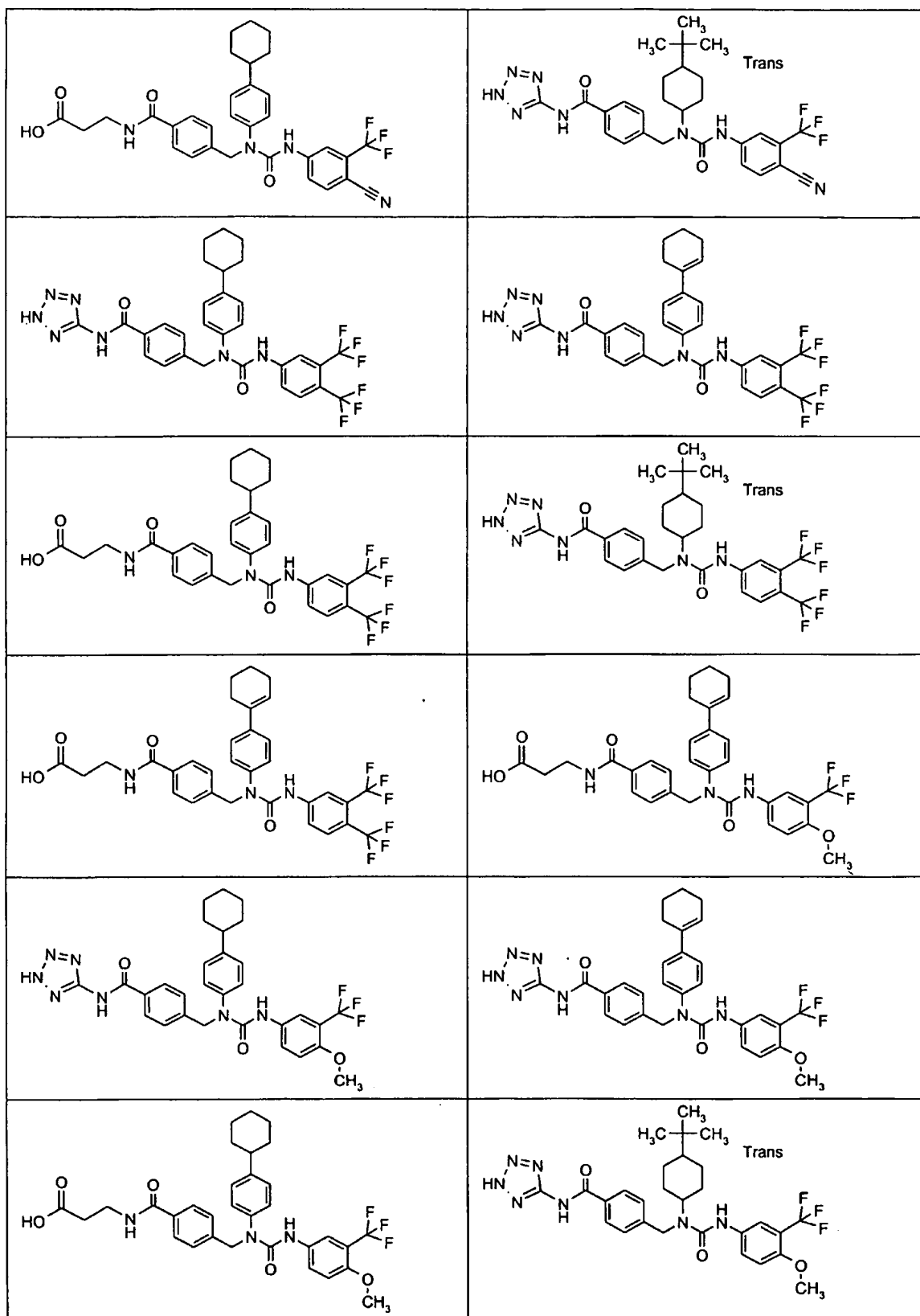
5 broadly enabled by the preceding disclosure.

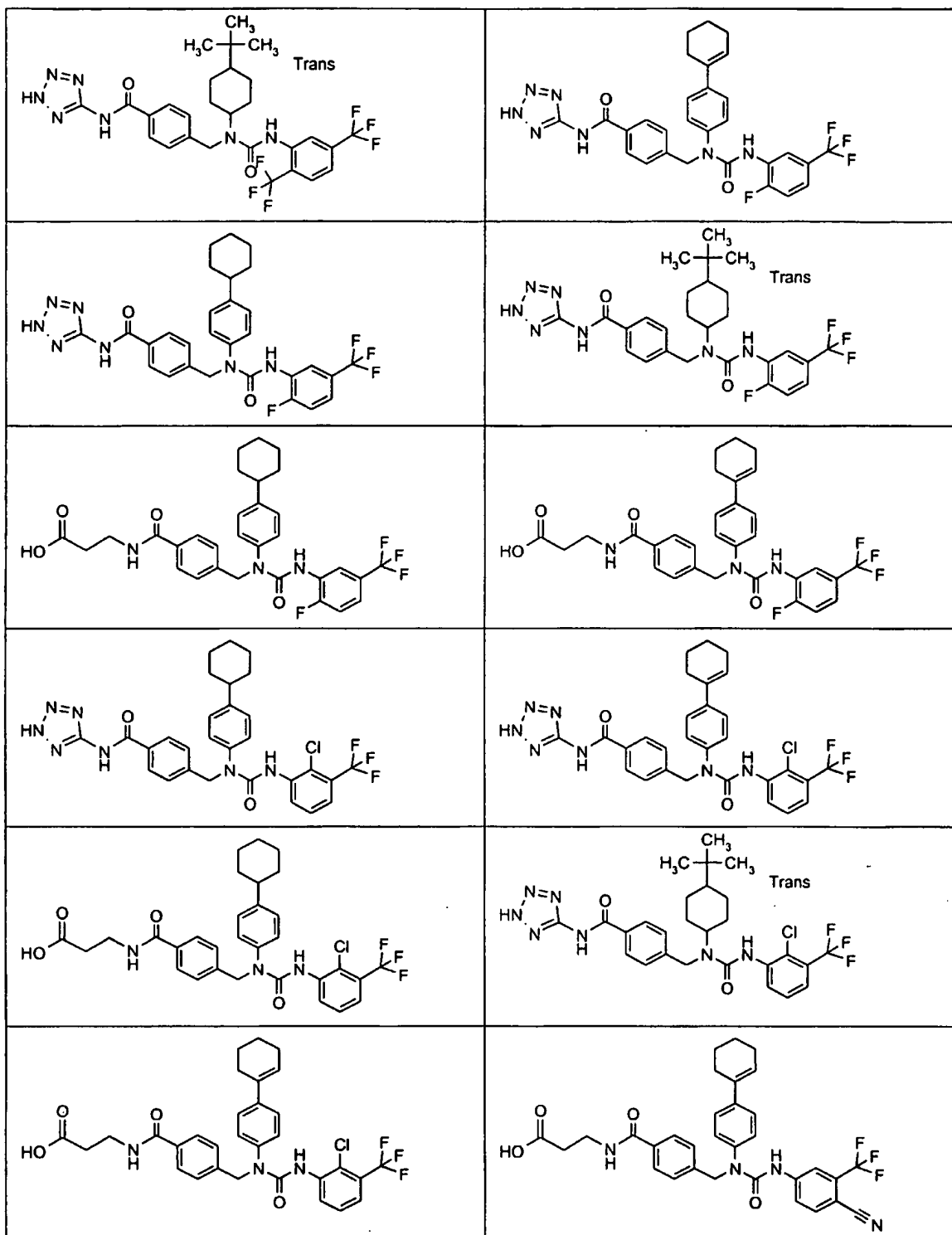
Accordingly, the invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive, and the scope of the invention is, therefore, indicated by the appending claims rather than by the foregoing description. All modifications, which

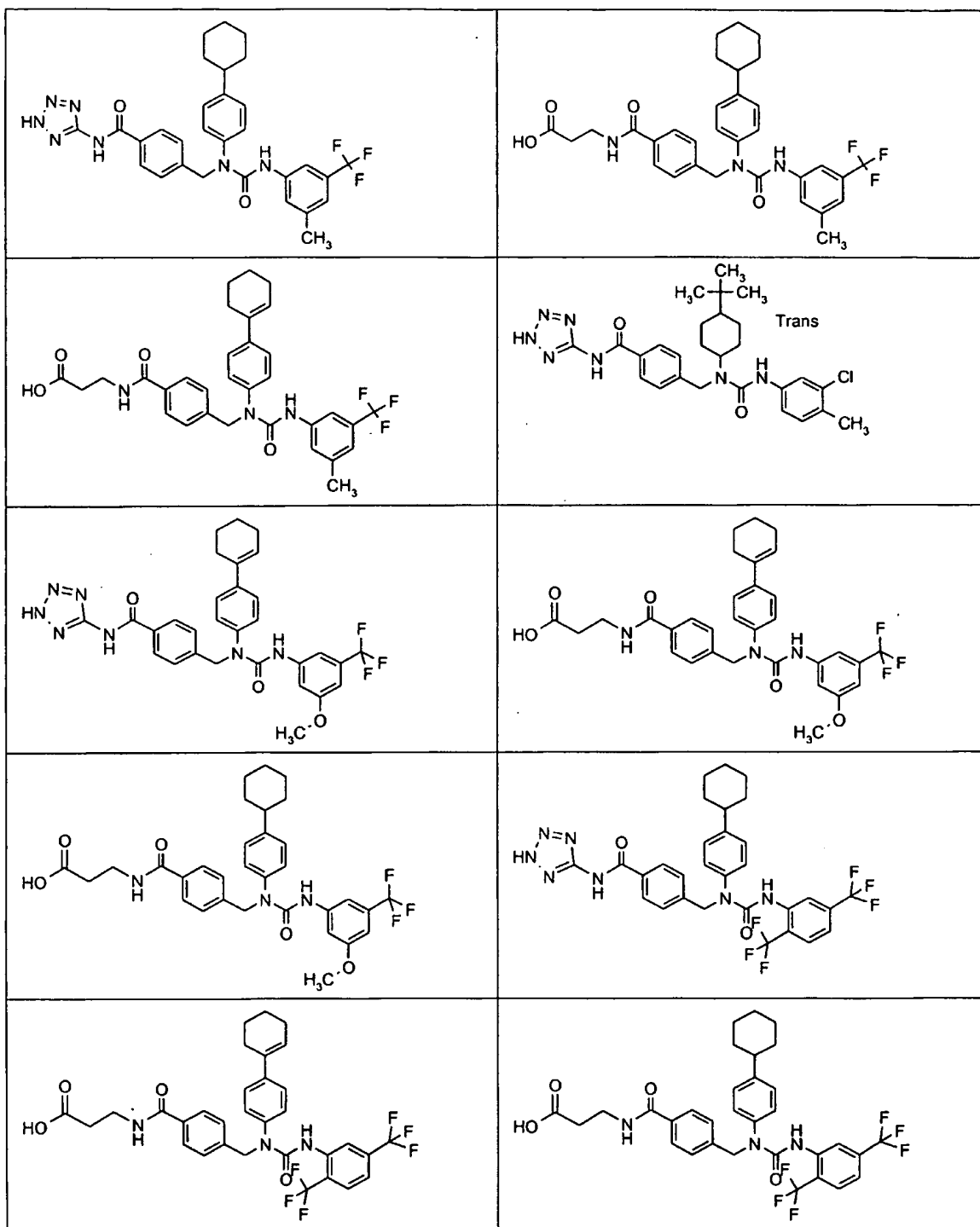
10 come within the meaning and range of the lawful equivalency of the claims, are to be embraced within their scope.

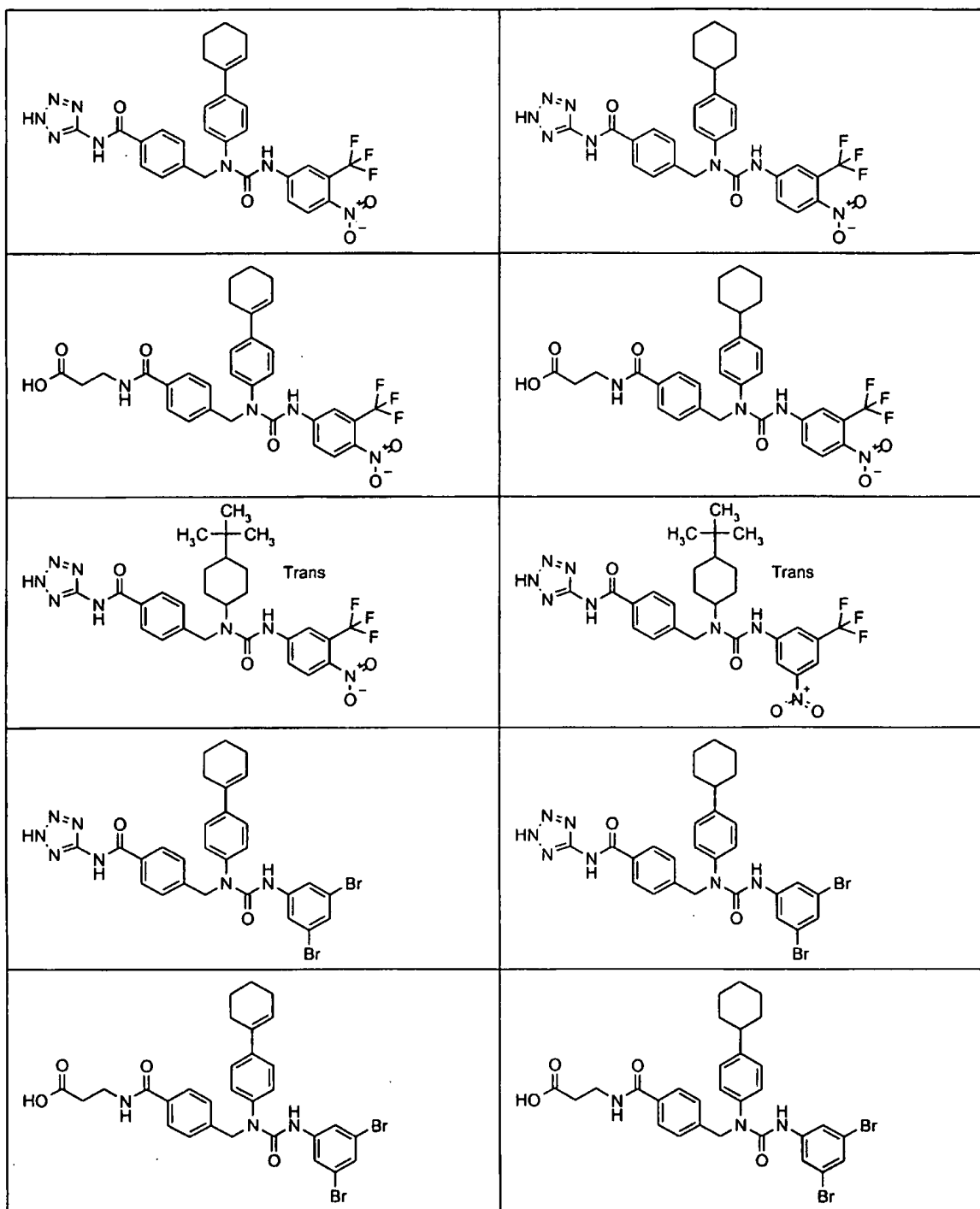


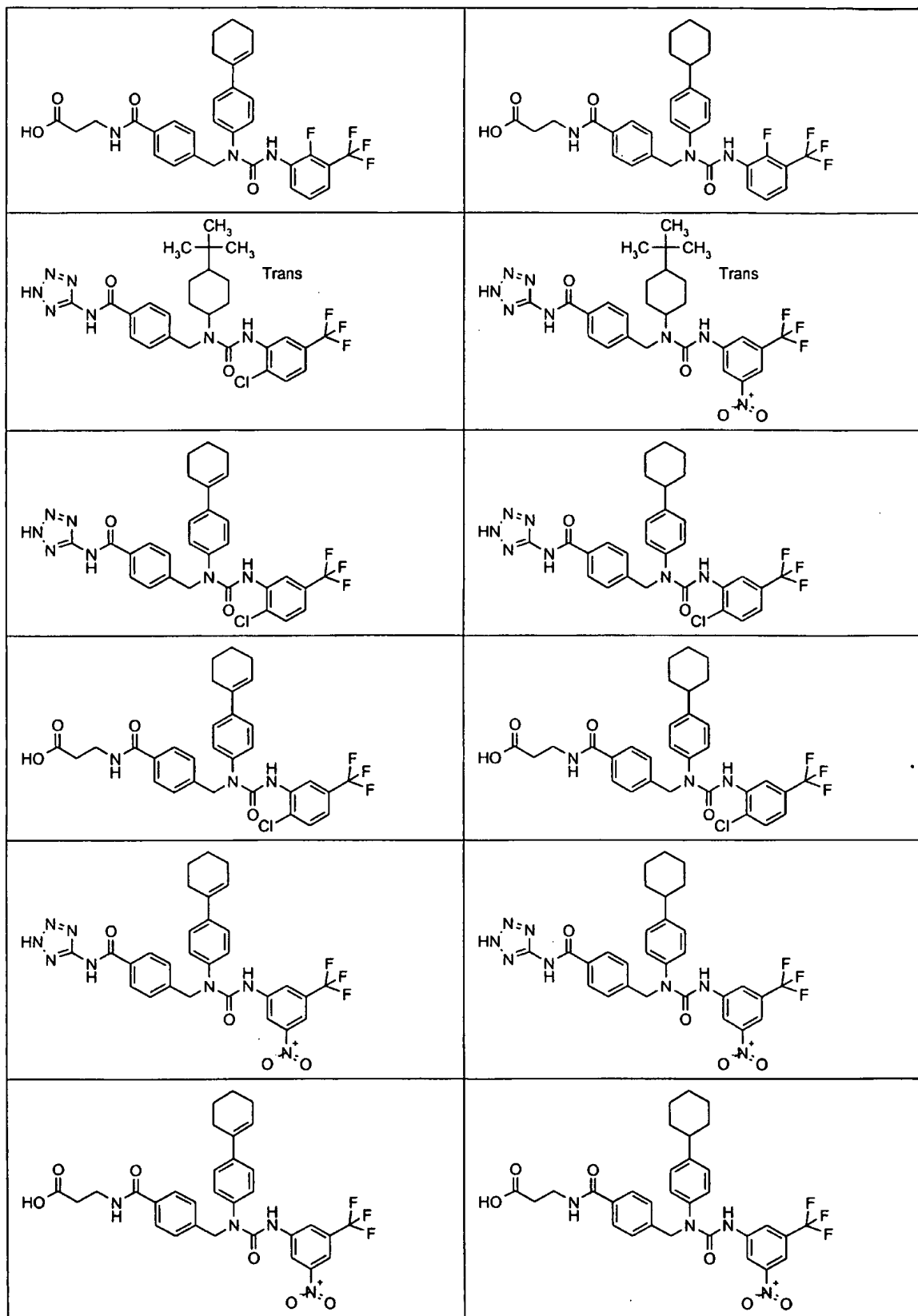


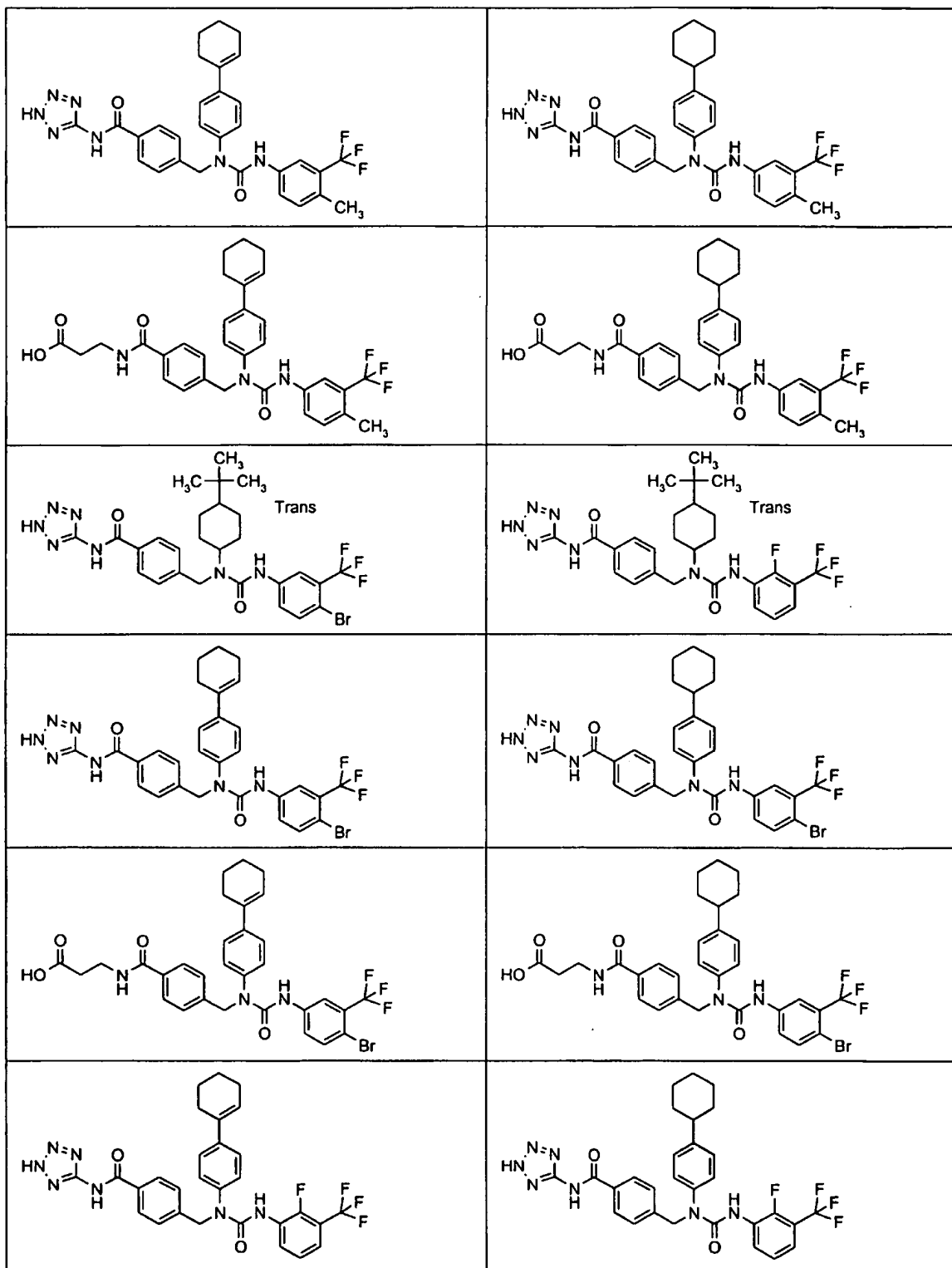


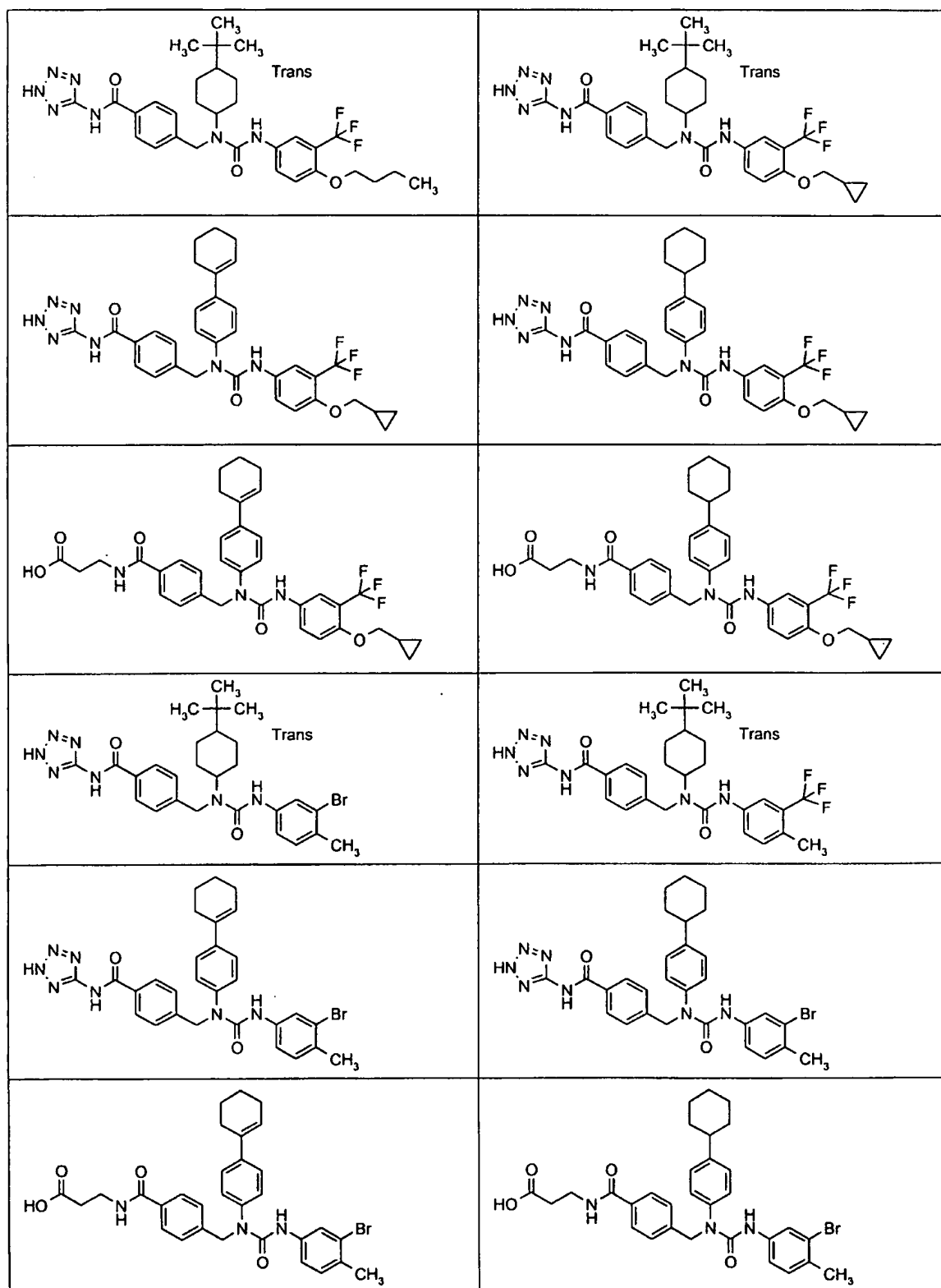


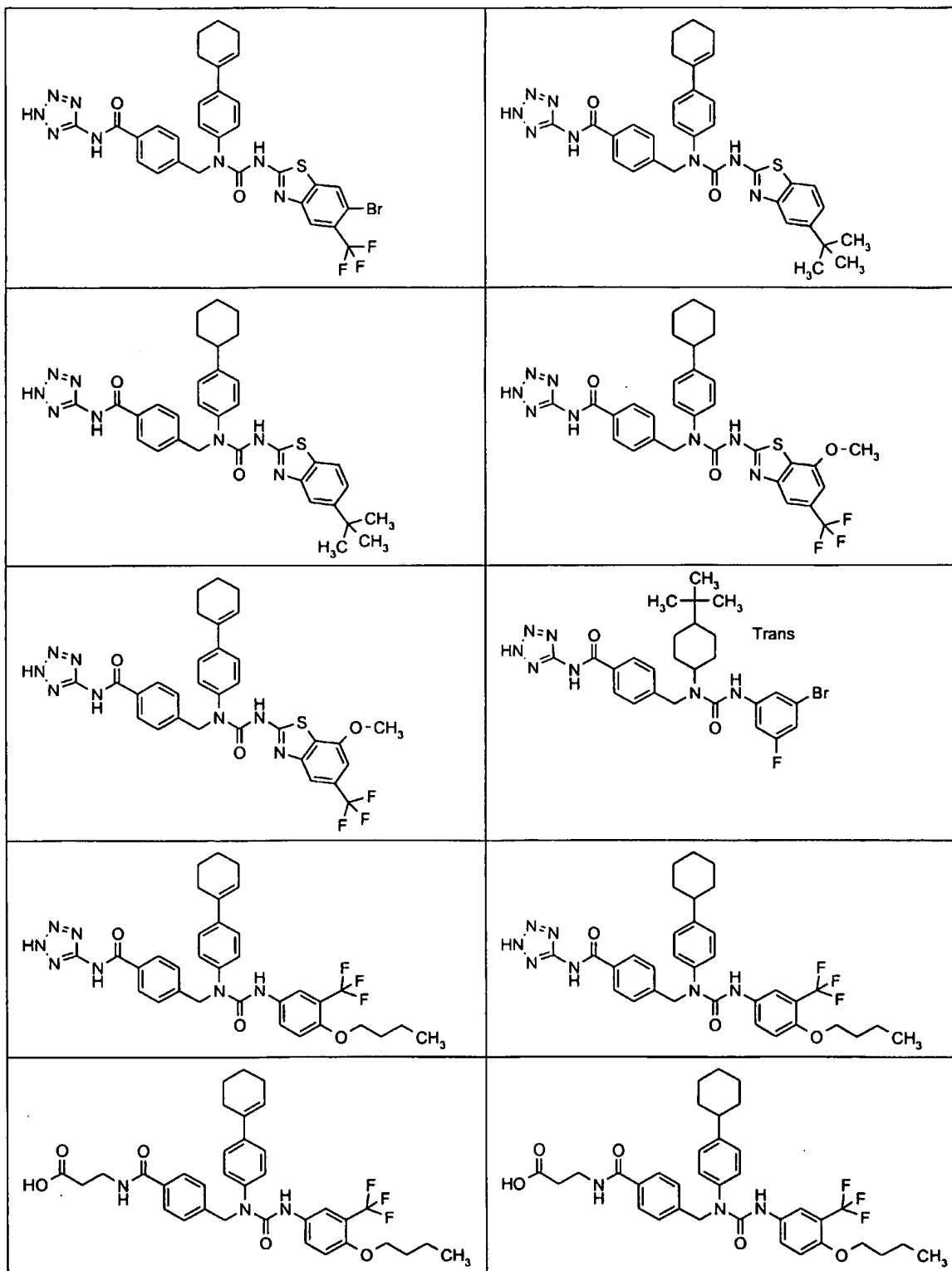


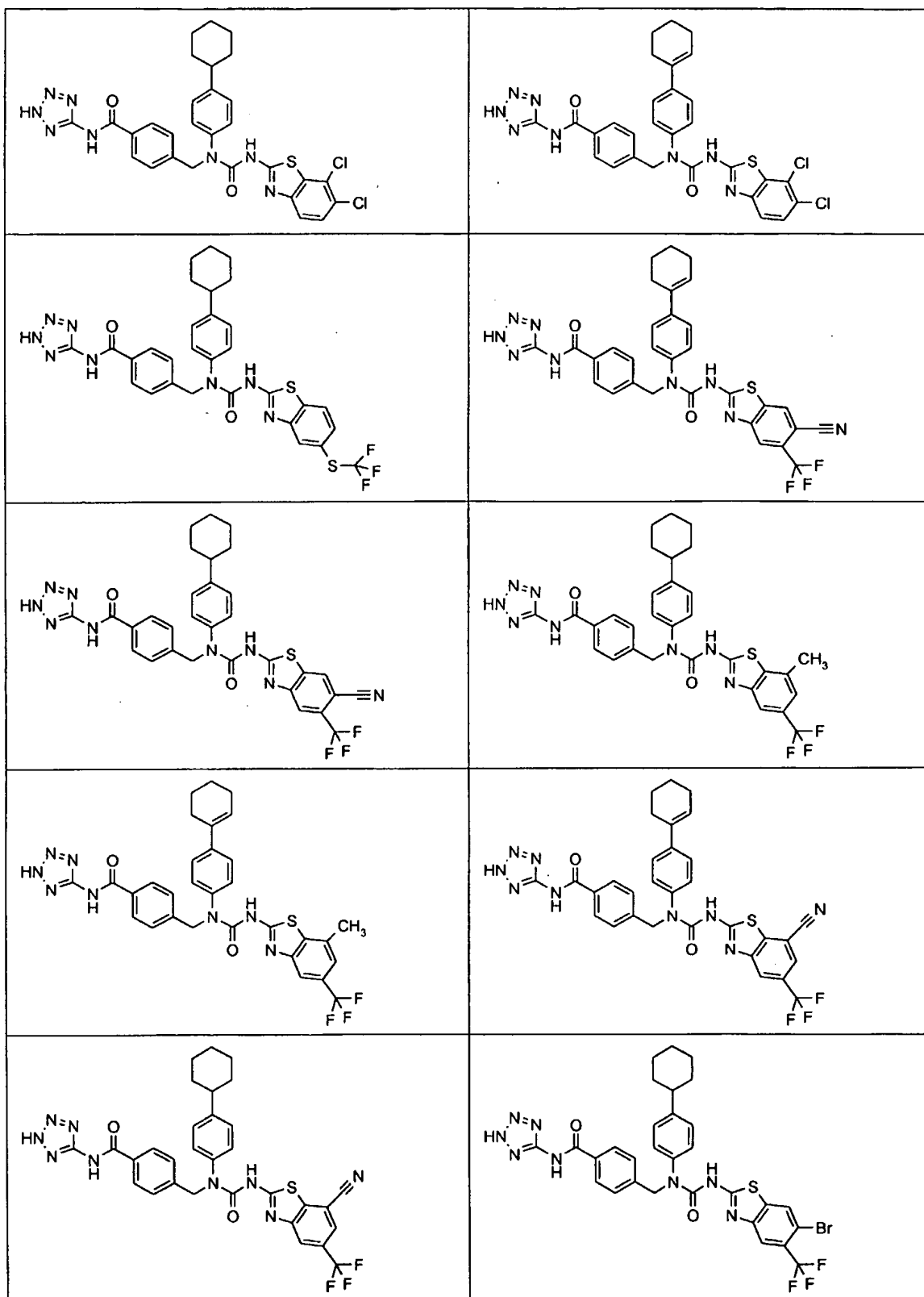


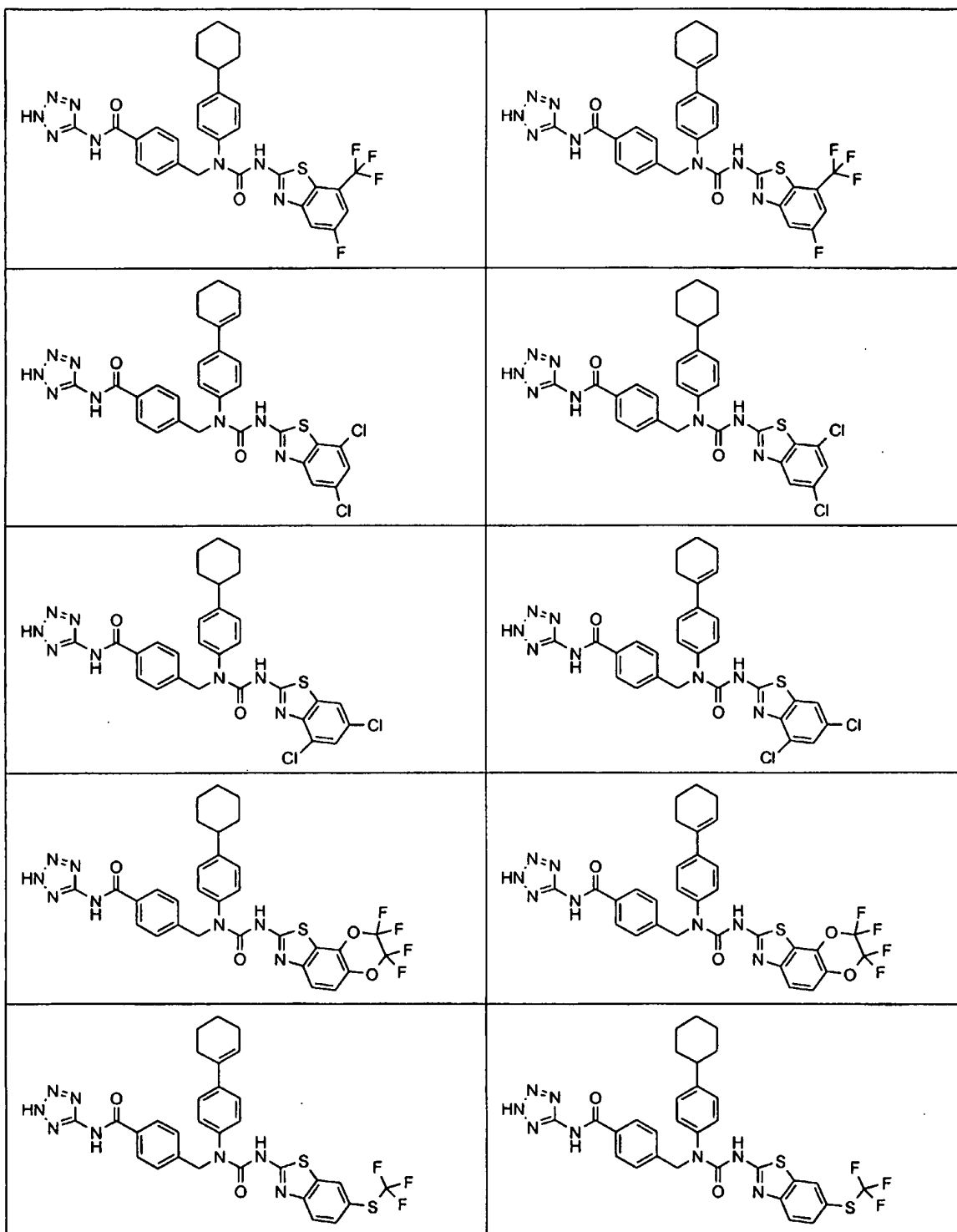


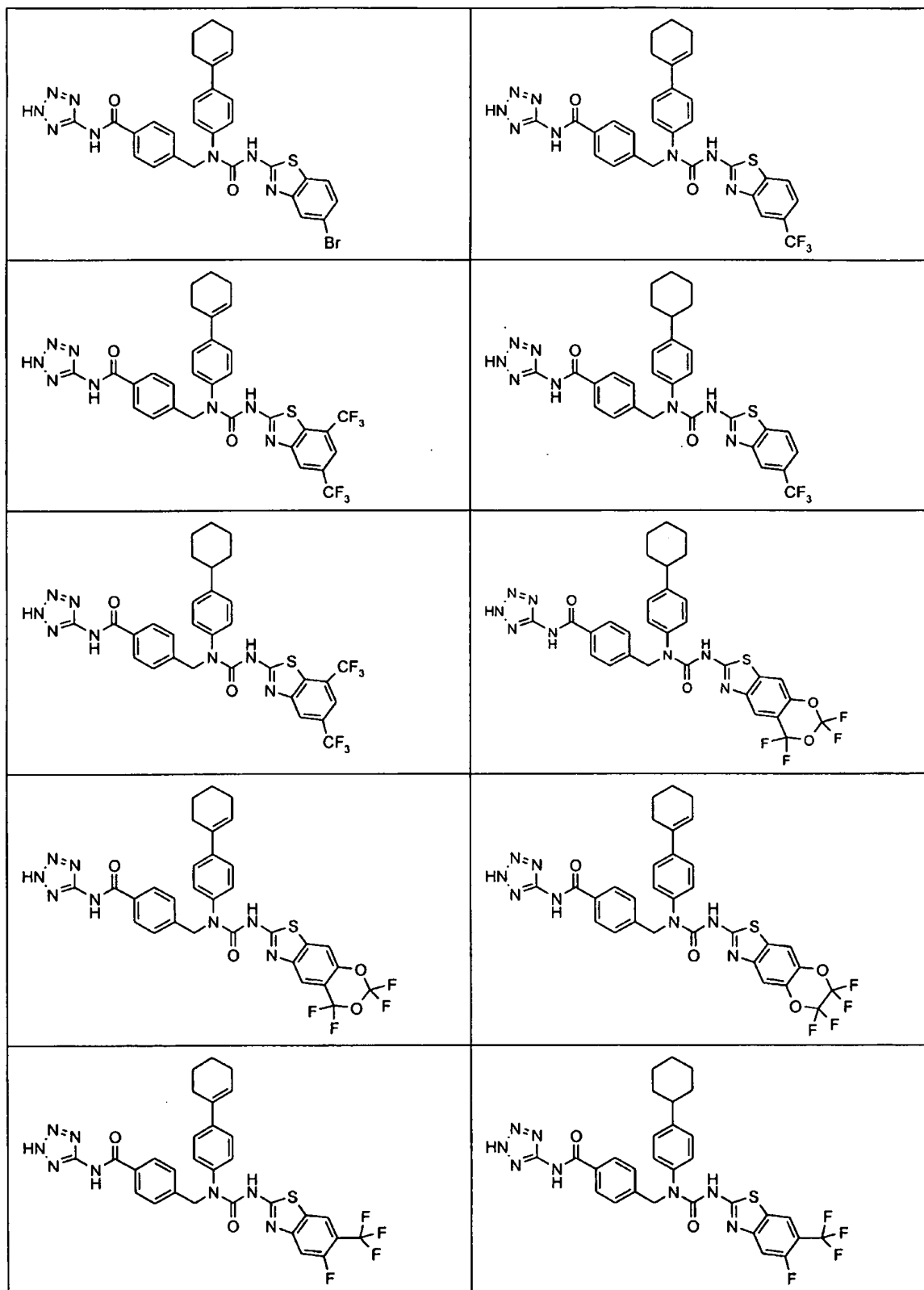


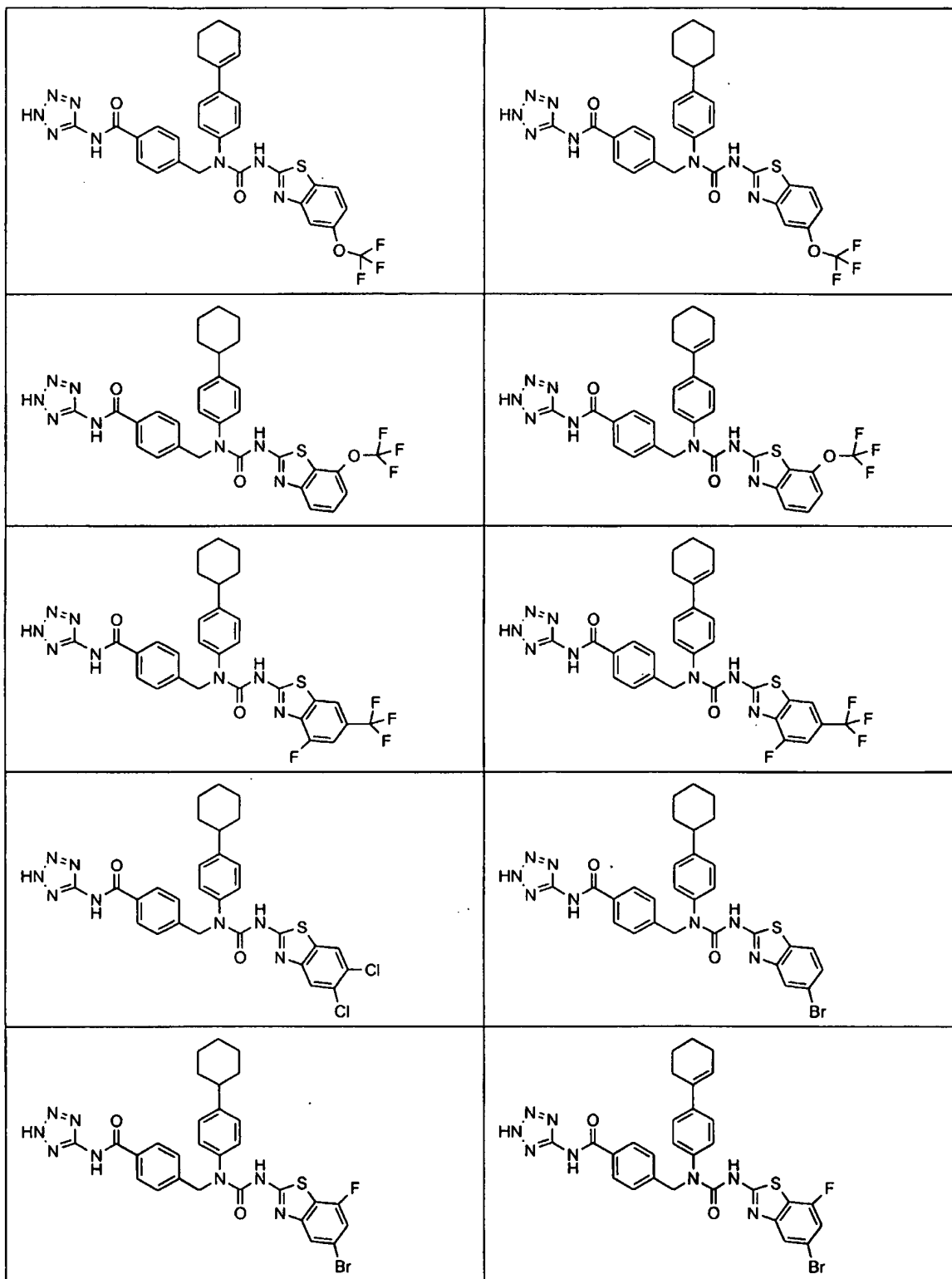


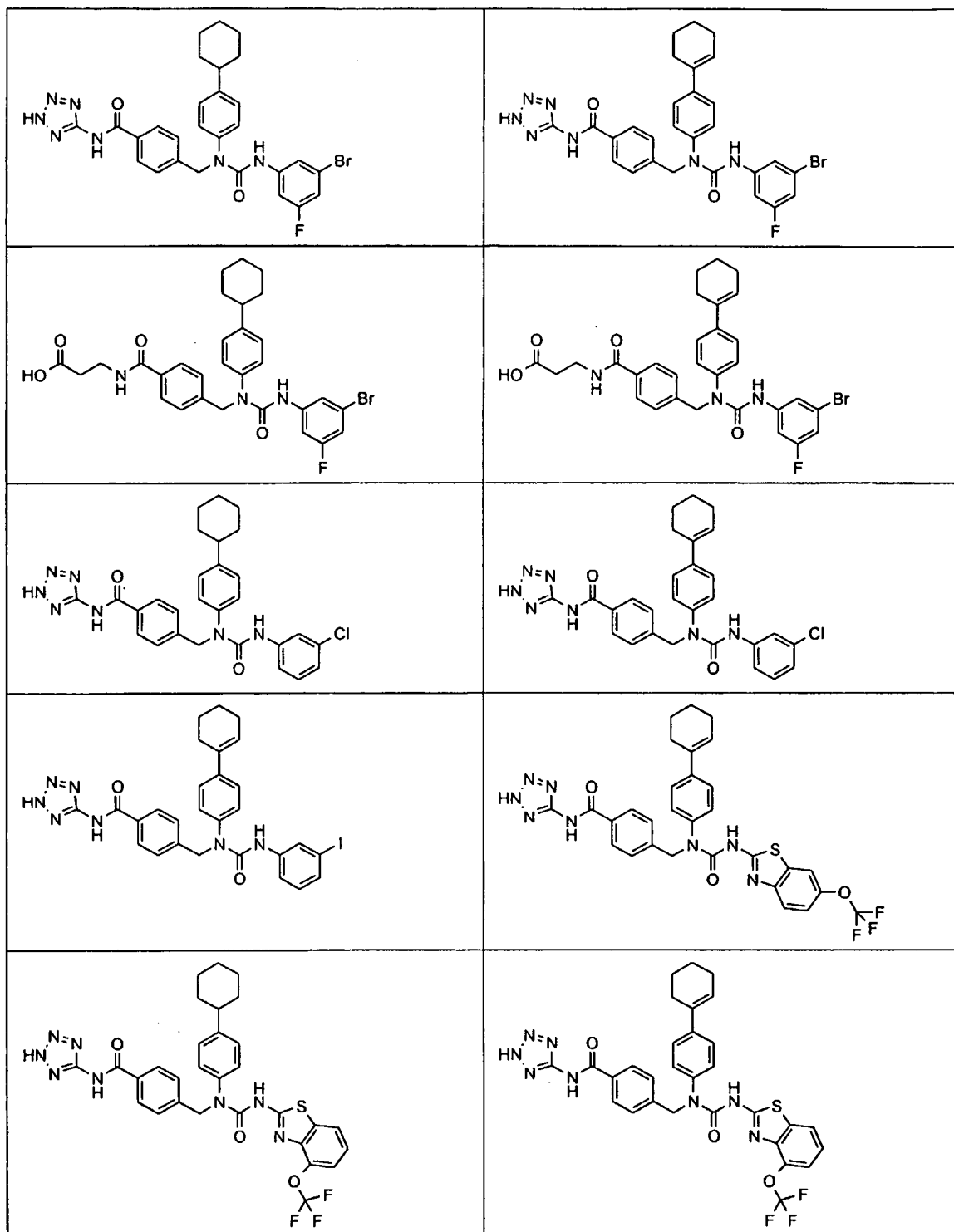


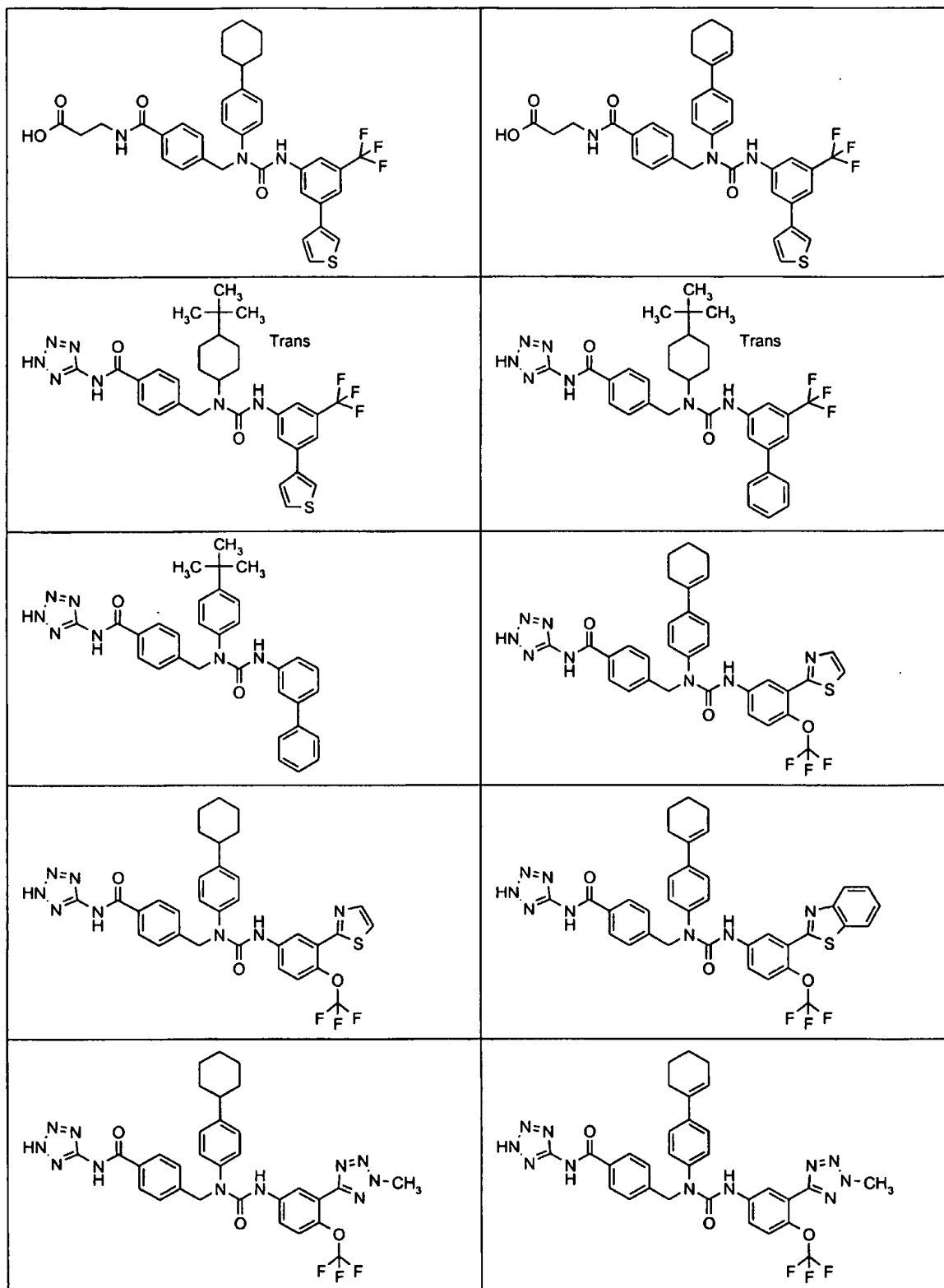


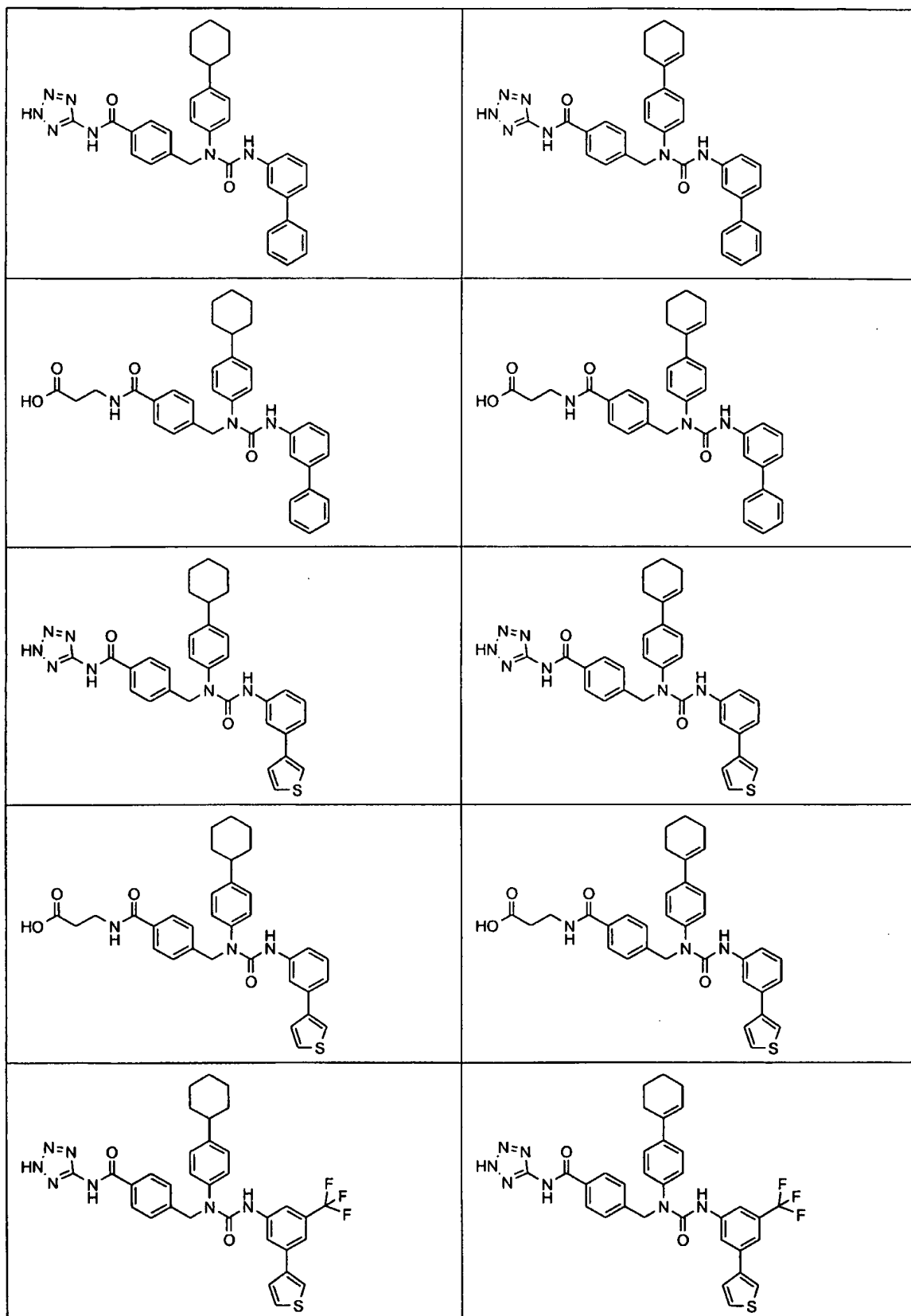


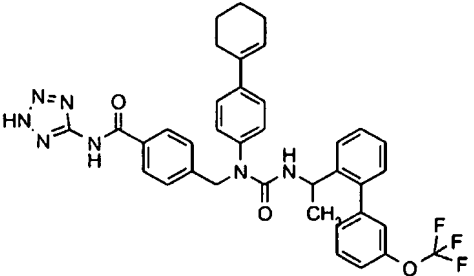
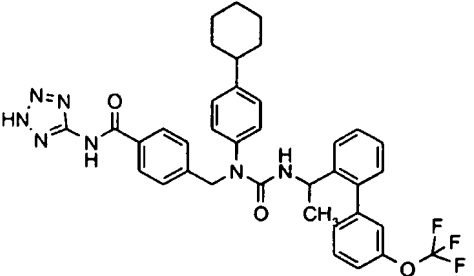
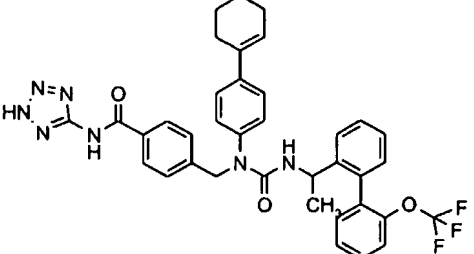
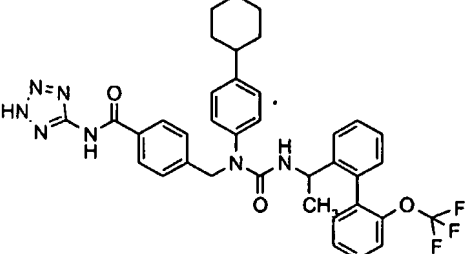
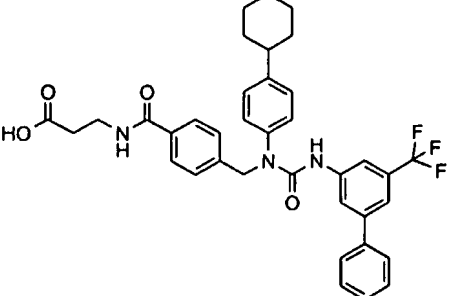
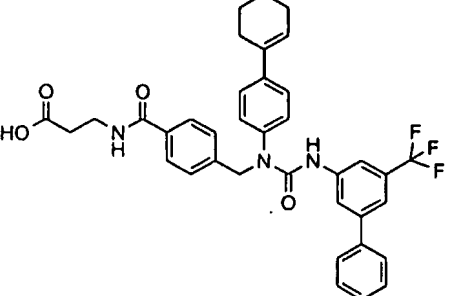
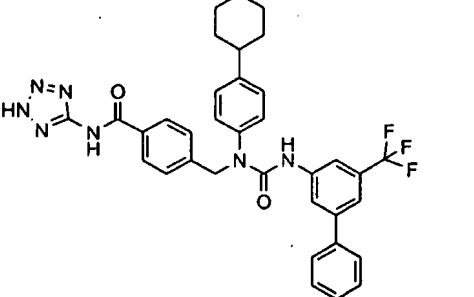
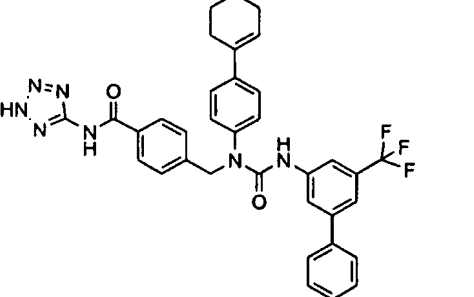
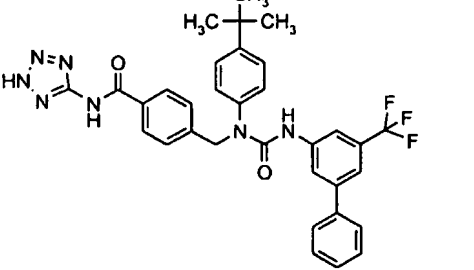
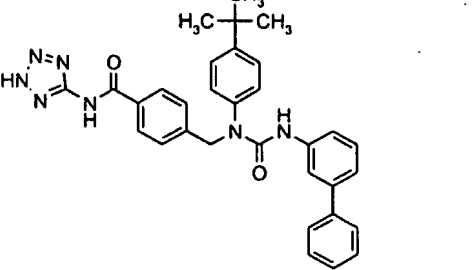


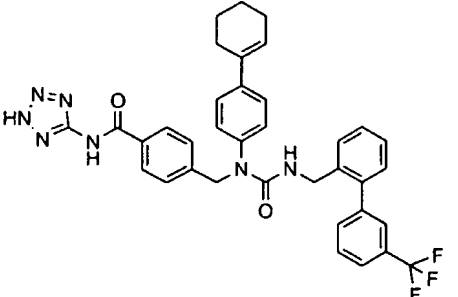
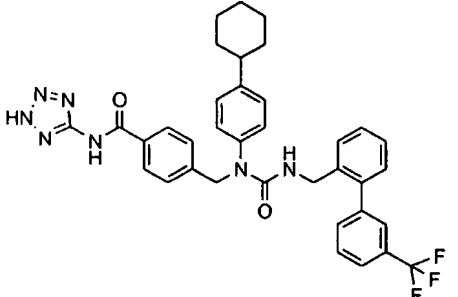
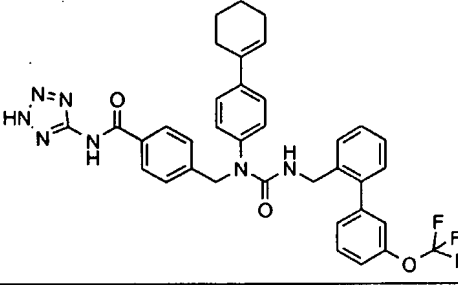
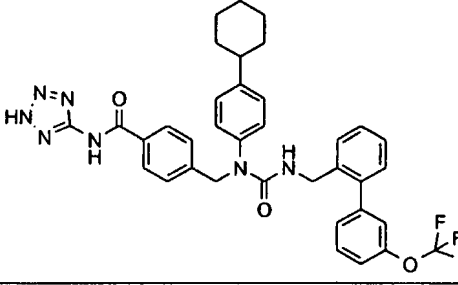
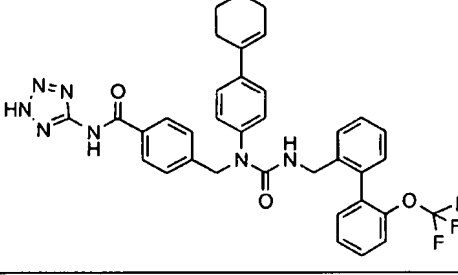
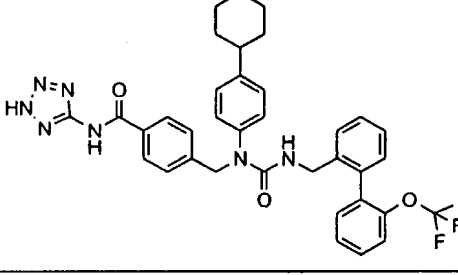
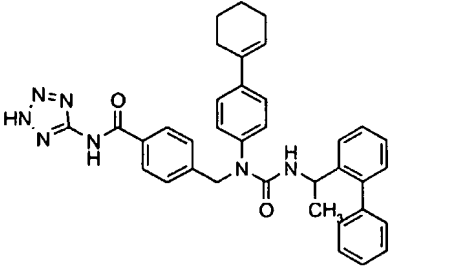
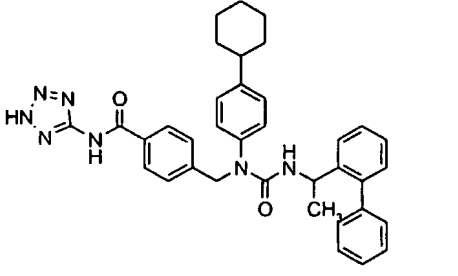
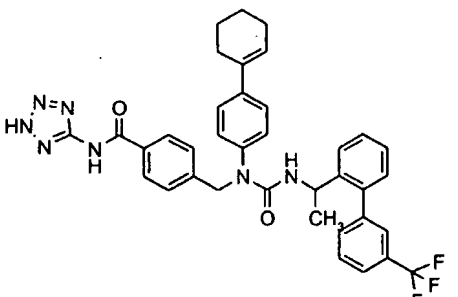
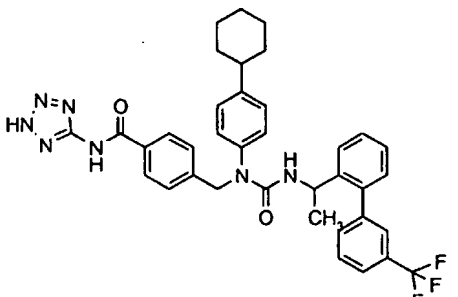


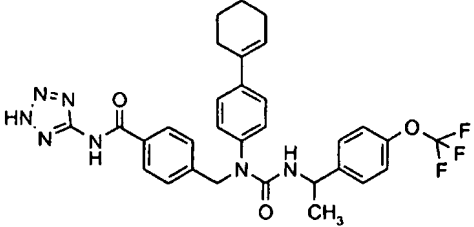
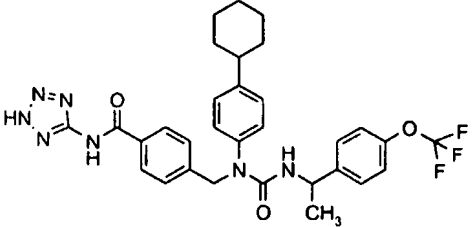
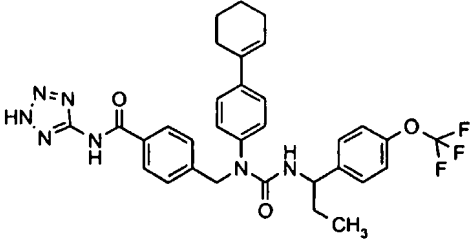
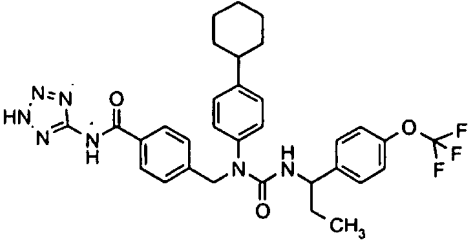
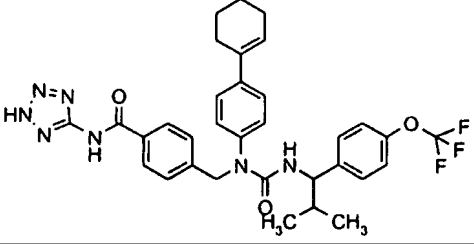
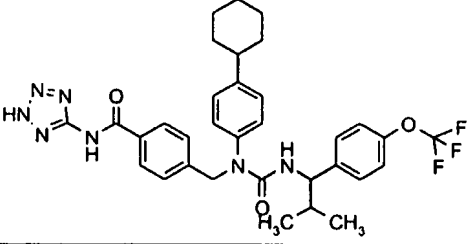
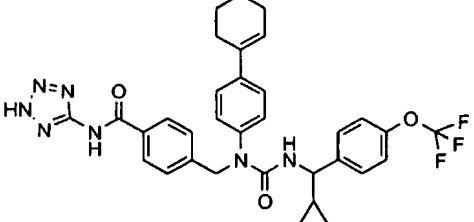
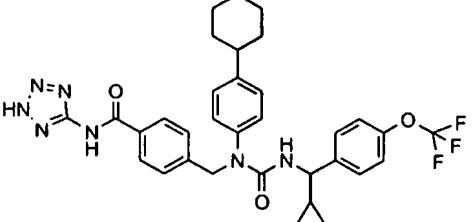
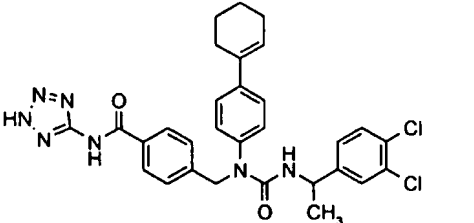
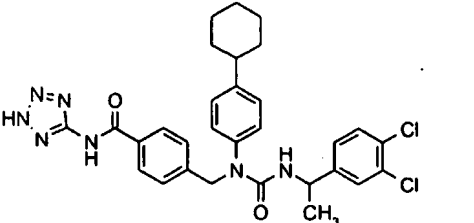


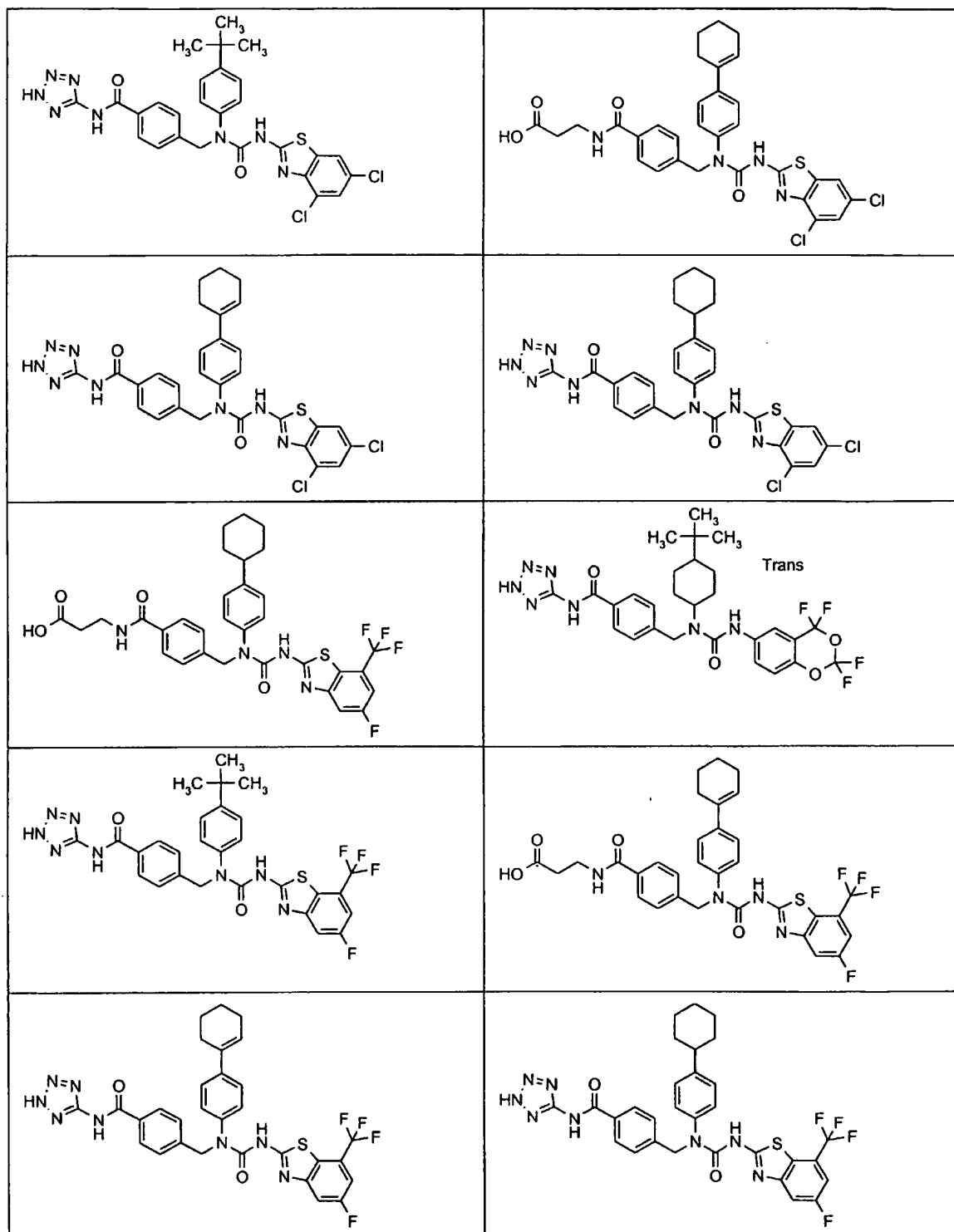


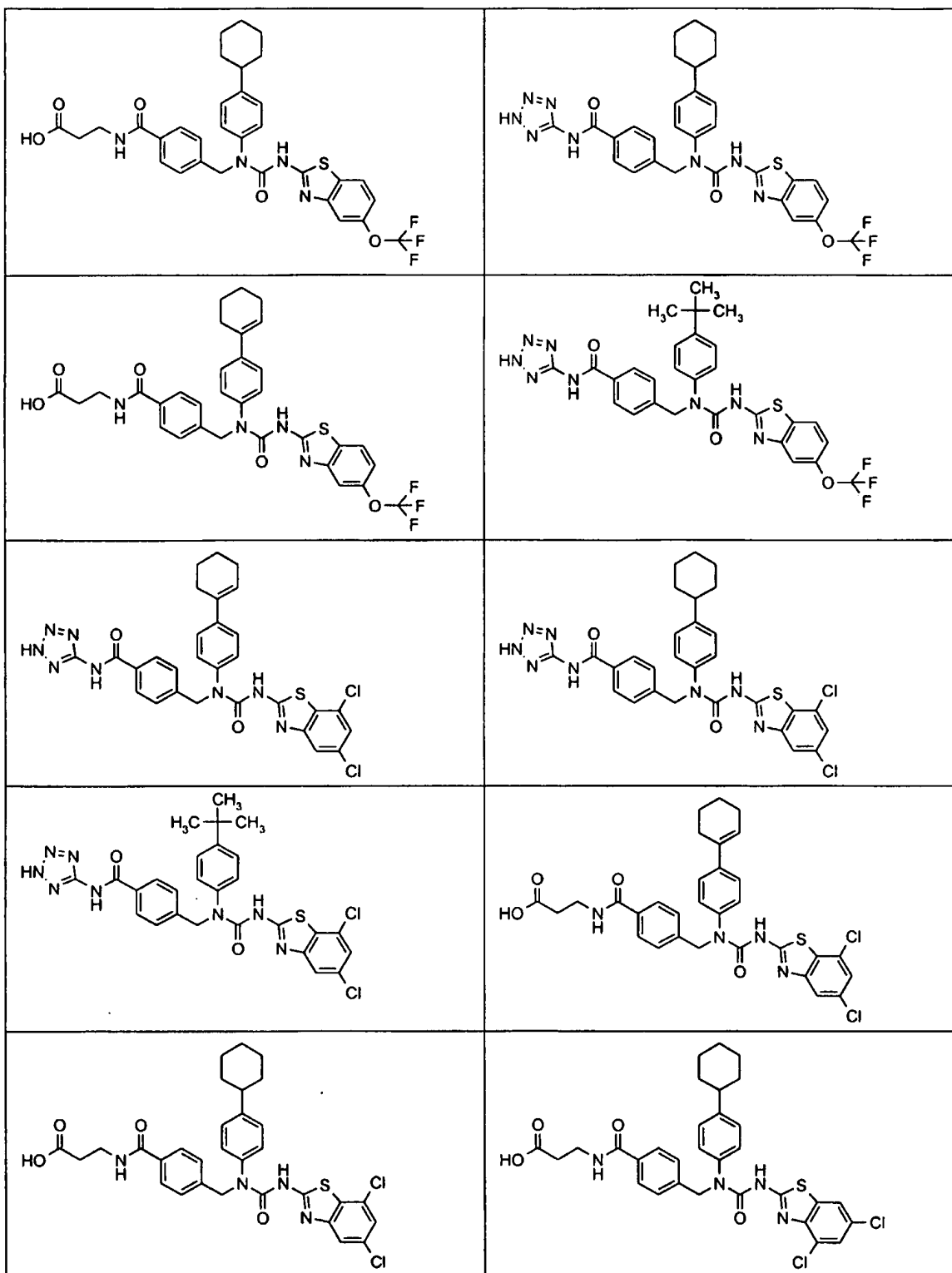


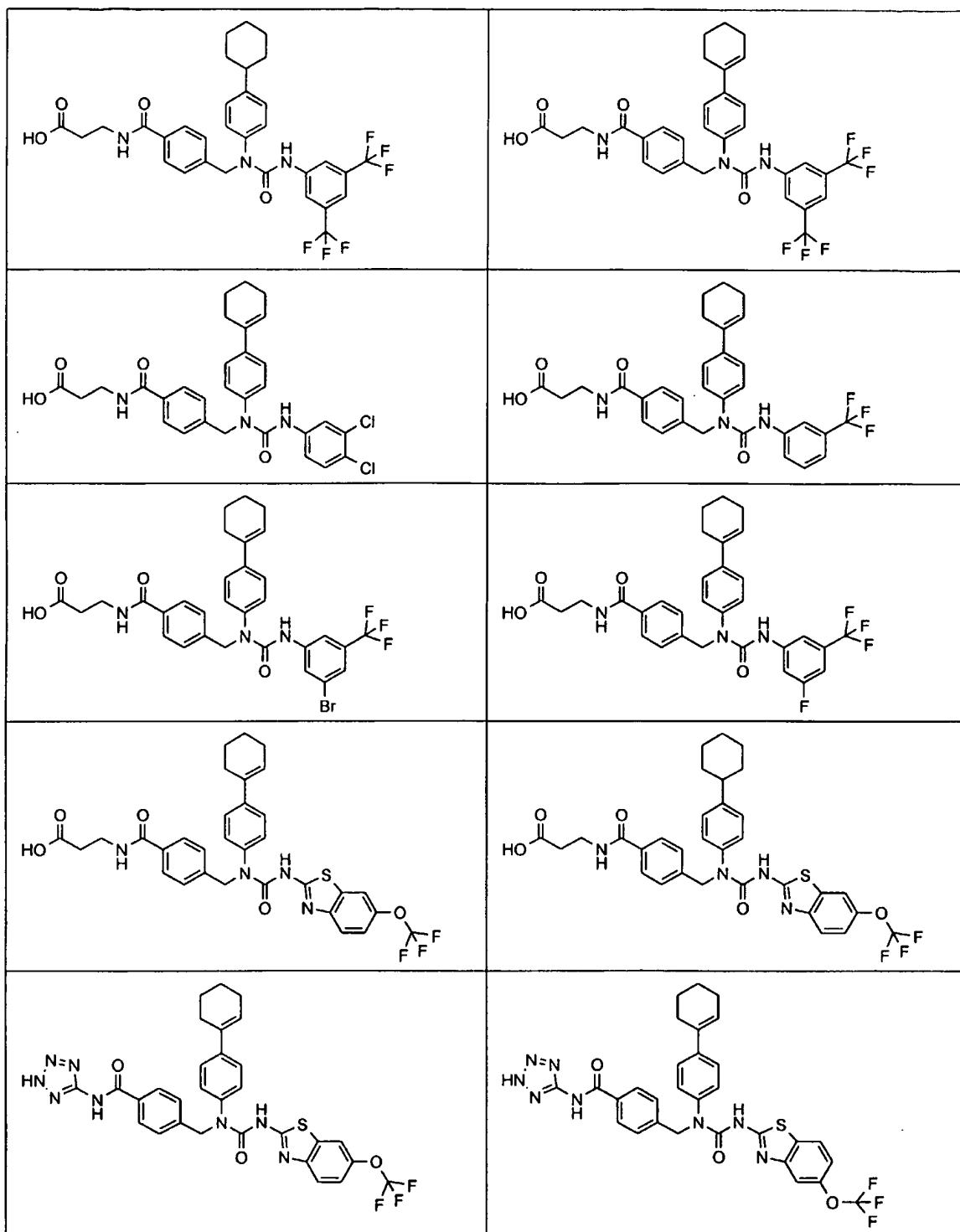
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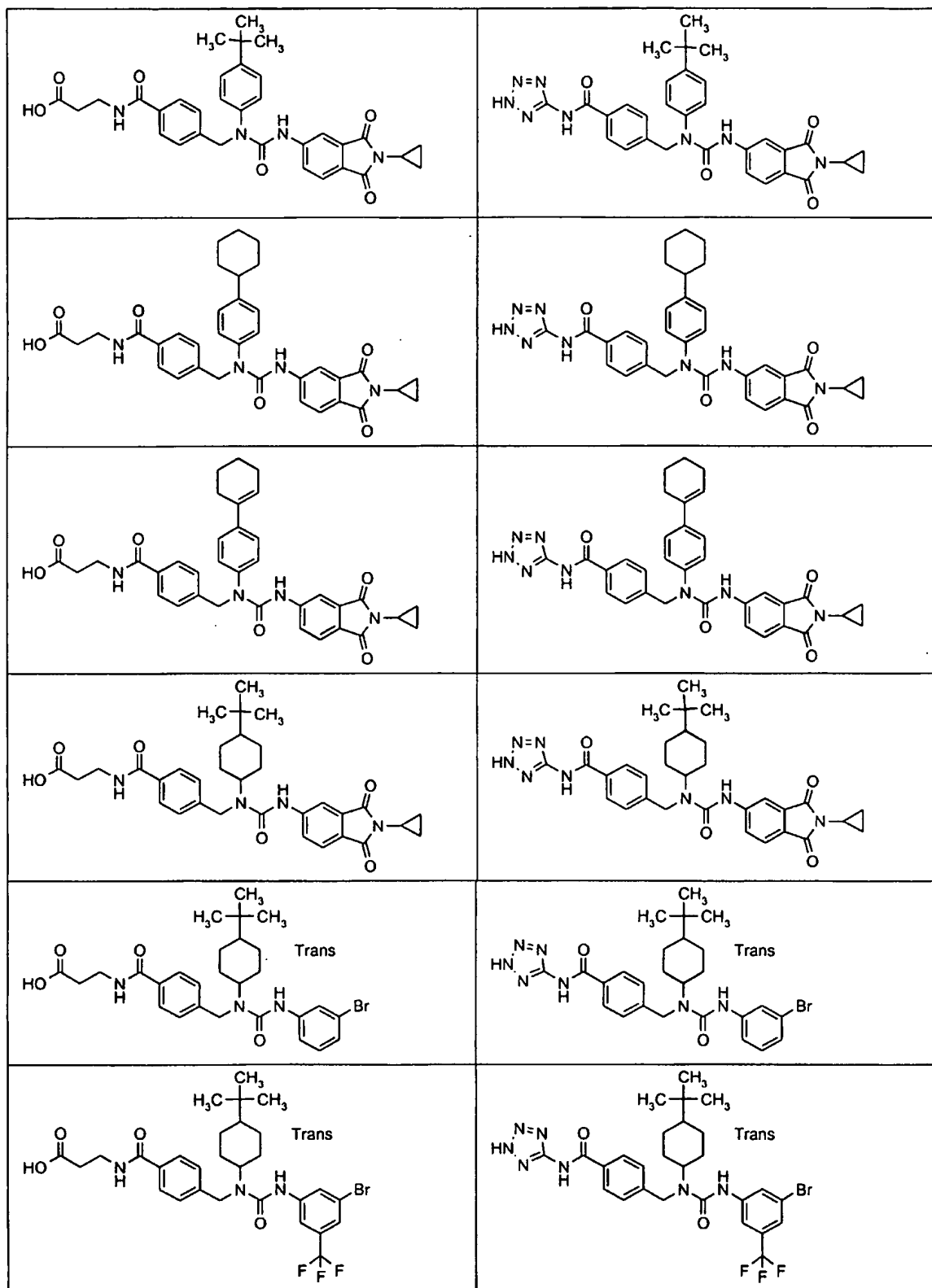
	
	
	
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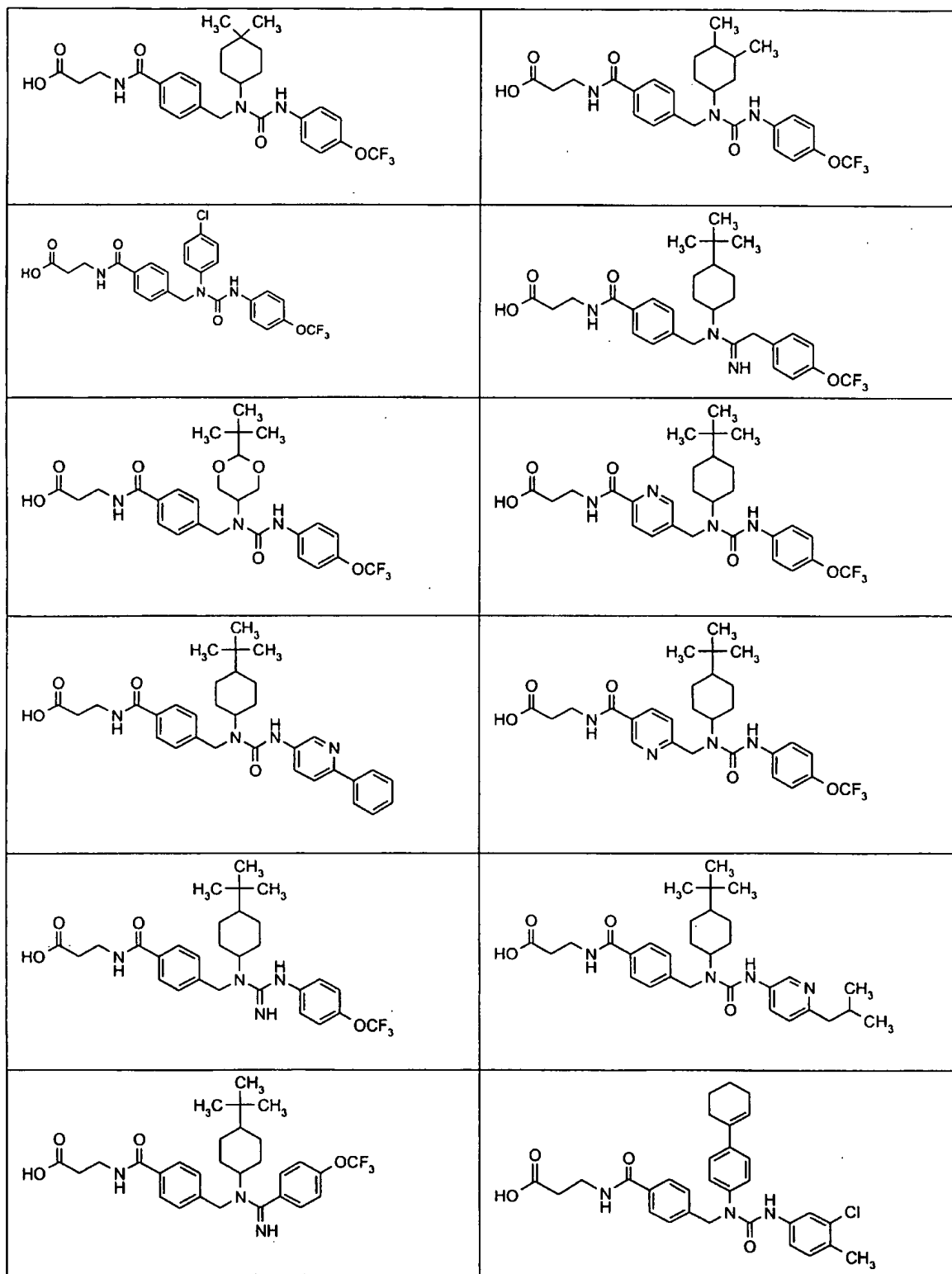
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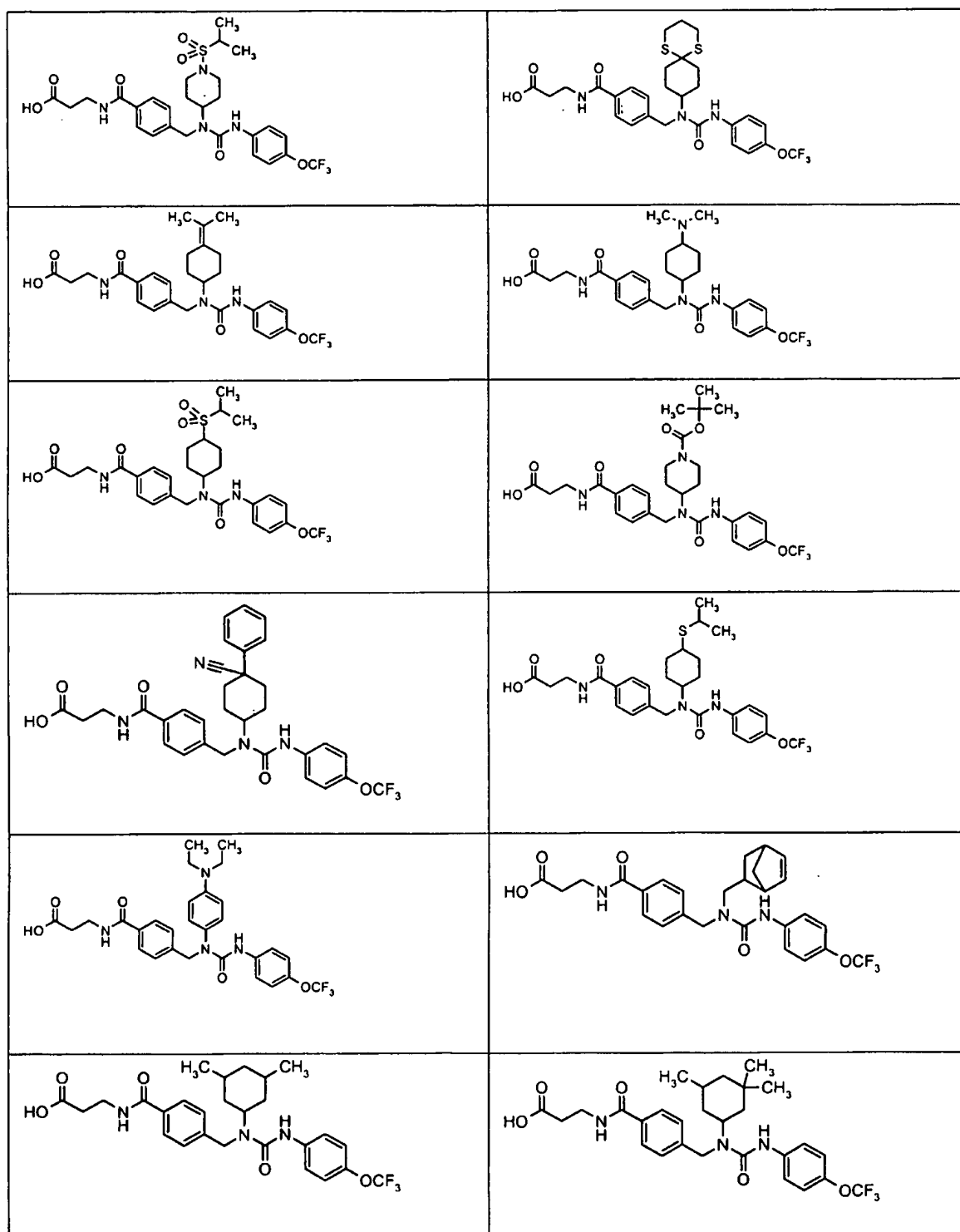




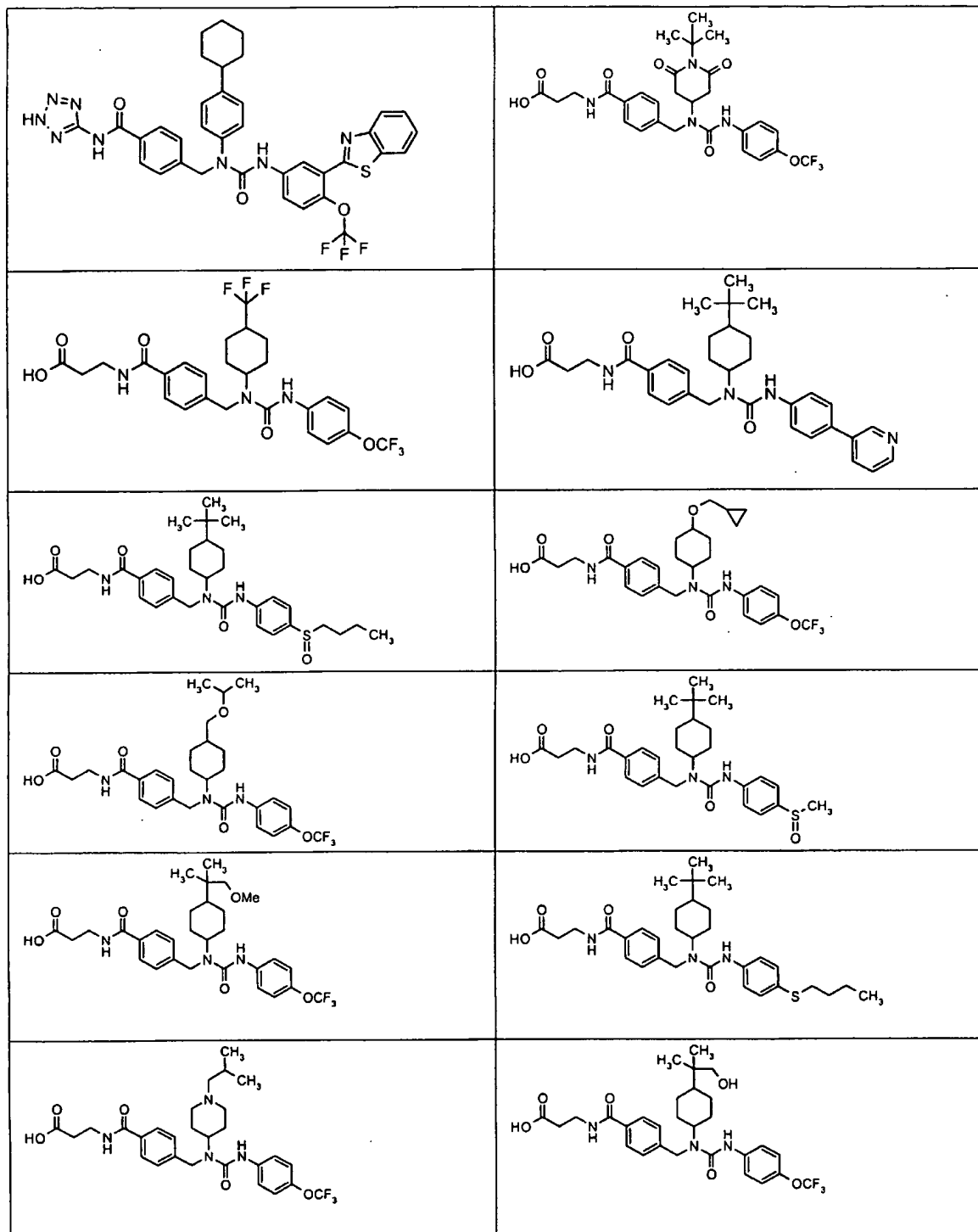




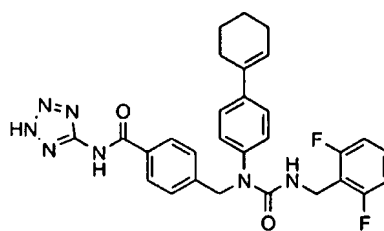
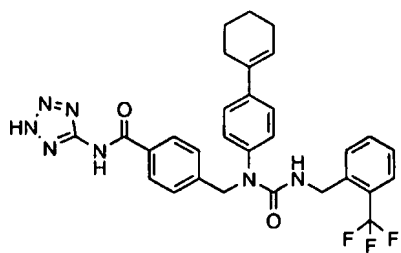
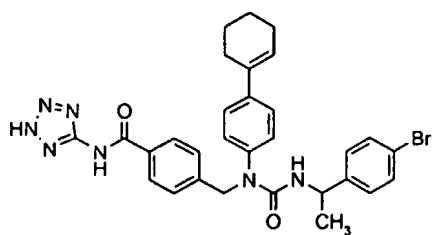


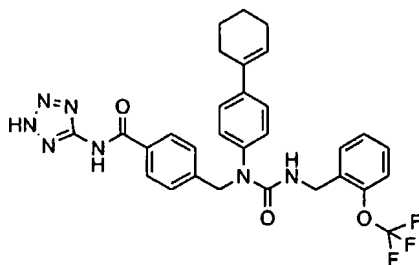
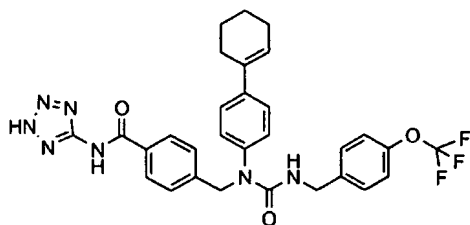
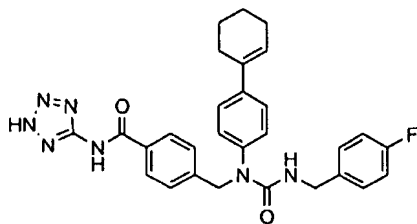
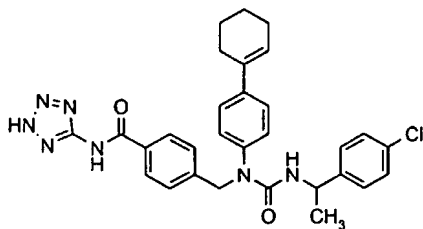
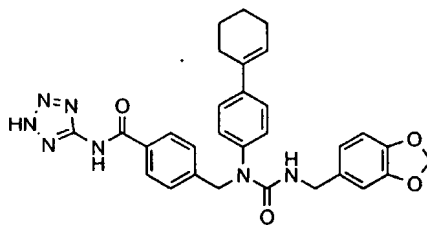
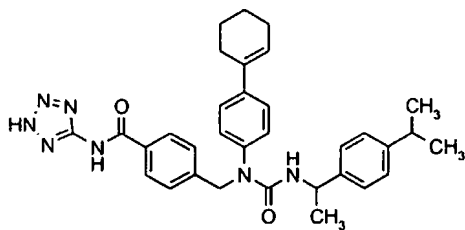
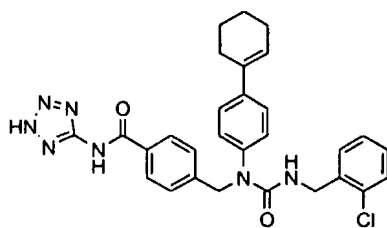
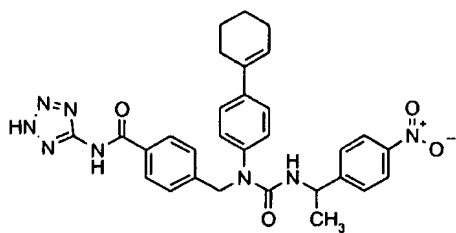
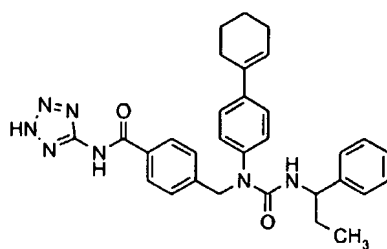
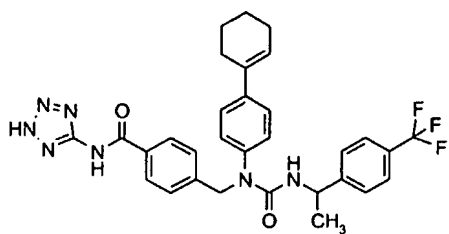
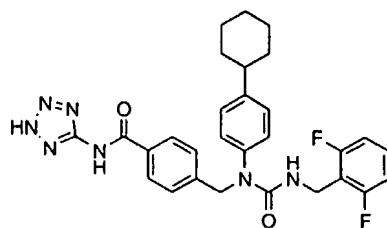
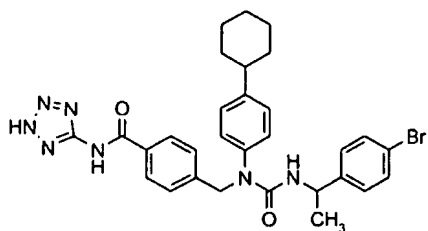


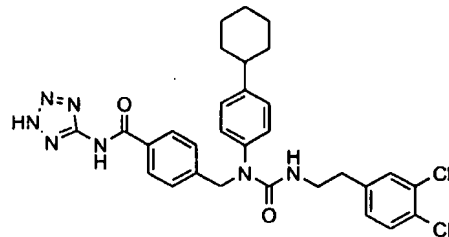
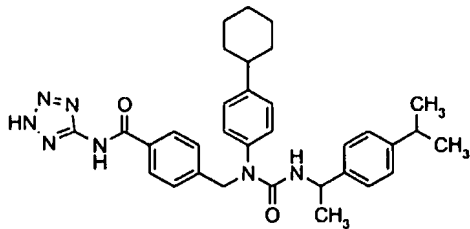
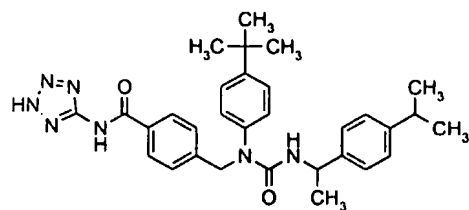
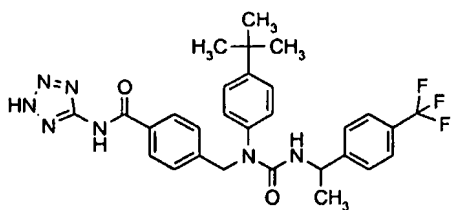
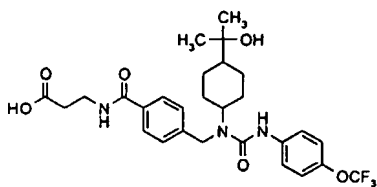
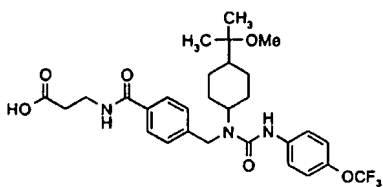
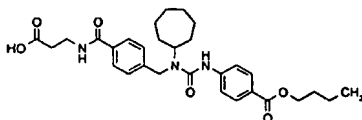
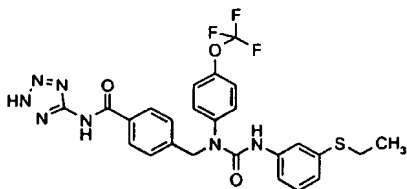
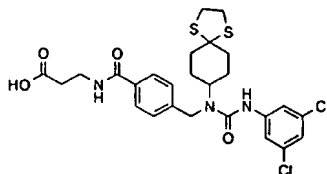
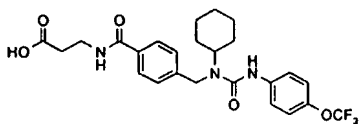
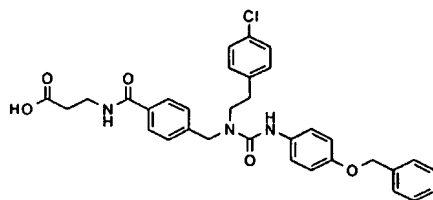
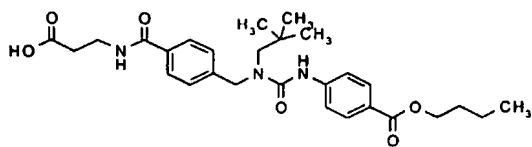
Furthermore, the following preferred compounds according to the invention may be prepared according to the general procedures set forth in the foregoing description:



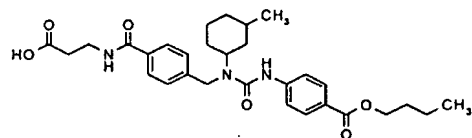
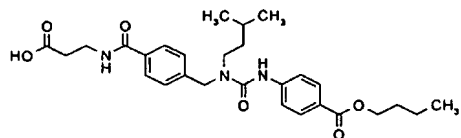
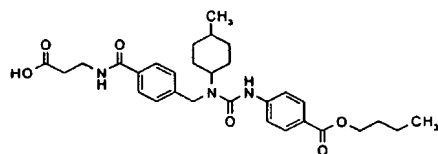
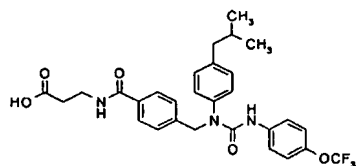
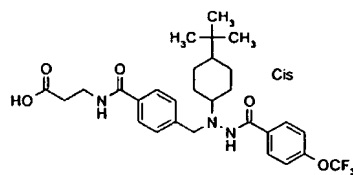
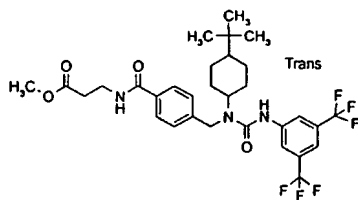
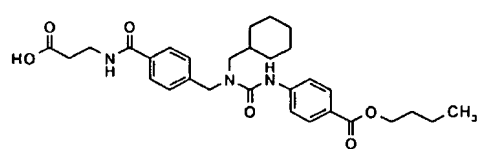
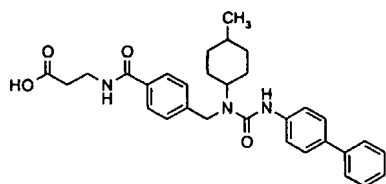
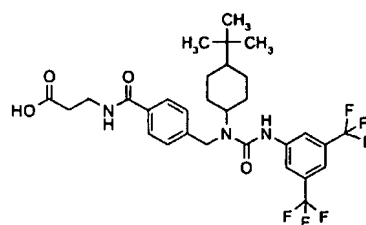
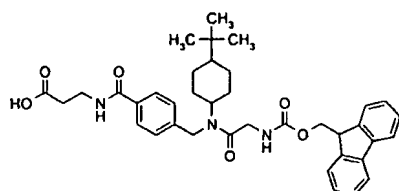
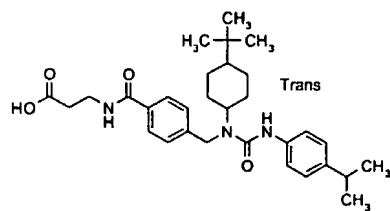
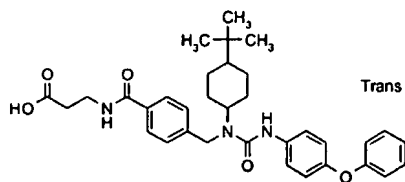
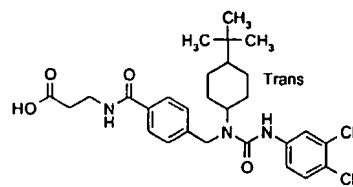
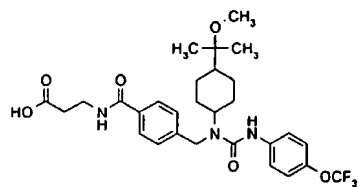
500







Furthermore, the following compounds according to the invention are preferred:



borohydride (0.88 g, 14 mmol) in methanol (10 mL) was slowly added, and the reaction mixture stirred for a further 60 min. The reaction mixture was then poured into ice water (100 mL) and pH adjusted to 2 using 1M aqueous hydrochloric acid. The crude product was collected by filtration and dried in a vacuum oven overnight. The crude product was taken up in
5 DMF/ethyl acetate (1:1, 5 mL) and passed through a silica gel column using 5% acetic acid/ethyl acetate as eluent. Pure fractions were pooled and evaporated to dryness. The yield of 4-[1-(4-*tert*-butylphenylamino)ethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide was 1.12 g (71%).

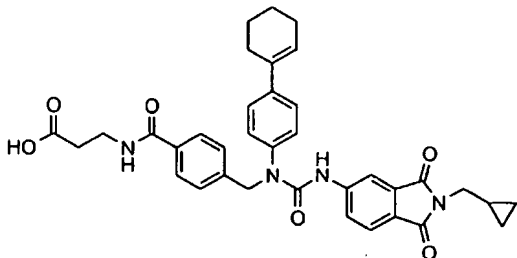
¹H NMR (DMSO-*d*₆): δ 1.15 ppm (s, 9H); 1.43 (d, 3H); 4.52 (q, 1H); 6.09 (bs, 1H); 6.41 (d,
10 2H); 7.00 (d, 2H); 7.56 (d, 2H); 8.04 (d, 2H); 12.30 (s, 1H).

Step 3: 4-[1-(4-*tert*-Butylphenylamino)ethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (100 mg, 0.28 mmol) and 4-trifluoromethoxyphenyl isocyanate (70 mg, 0.30 mmol) was dissolved in DMF (0.6 mL) and the solution was heated to 80°C for 3 hours. The mixture was cooled to room
15 temperature and subsequently taken to dryness using rotary evaporation. The residual oil was dissolved in a minimum of DMF/acetonitrile (1:1), and submitted to preparative HPLC purification. Pure fractions were pooled and concentrated to dryness to afford 10 mg (8%) of the title compound.

20 HPLC-MS (method B): *m/z* = 568.0, *R*_t = 5.31 min.

EXAMPLE 645

3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-benzoylamino}propionic acid



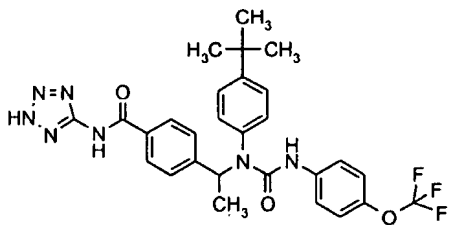
5

HPLC-MS (method B): m/z = 621.0, R_t = 7.32 min.

EXAMPLE 646

4-{1-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureido]ethyl}-*N*-(2*H*-tetrazol-5-yl)benzamide

10



Step 1: 4-Acetylbenzoic acid (4.00 g, 24.4 mmol), 5-aminotetrazole monohydrate (3.00 g, 2.91 mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride (7.00 g, 3.55 mmol) were dissolved in DMF (25 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was poured into ice-water, and the precipitate collected by filtration to afford 5.50 g (98%) of pure 4-acetyl-*N*-(2*H*-tetrazol-5-yl)benzamide after drying overnight in a vacuum oven.

¹H NMR (DMSO-*d*₆): δ 2.64 ppm (s, 3H); 8.12 (d, 2H), 8.20 (d, 2H). 12.60 (bs, 1H).

20

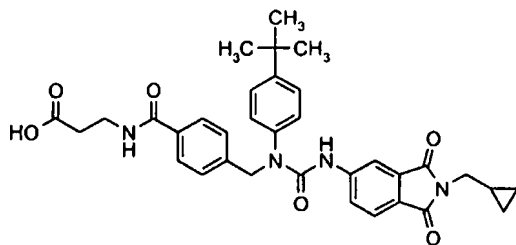
Step 2: 4-Acetyl-*N*-(2*H*-tetrazol-5-yl)benzamide (1.00 g, 4.32 mmol) and 4-*tert*-butylaniline were dissolved in THF (15 mL). Triethylamine (2.1 mL, 15.0 mmol) was added and the mixture was cooled to 0°C on an ice bath. Neat titanium tetrachloride (0.25 mL, 2.25 mmol) was added dropwise using a syringe assuring that the temperature was maintained close to 0°C. The mixture was then stirred overnight at room temperature. A solution of sodium cyano-

25

HPLC-MS (method B): m/z = 623.0, R_t = 7.45 min.

EXAMPLE 643

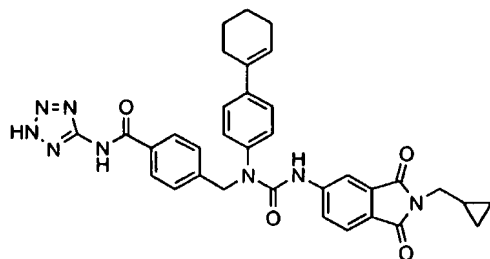
3-{4-[3-(N'-(Cyclopropylmethyl)phthalimid-4-yl)-1-(4-tert-butylphenyl)ureidomethyl]benzoyl-
amino}propionic acid



HPLC-MS (method B): m/z = 597.0, R_t = 6.89 min.

10 EXAMPLE 644

4-[3-(*N'*-[Cyclopropylmethyl]phthalimid-4-yl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

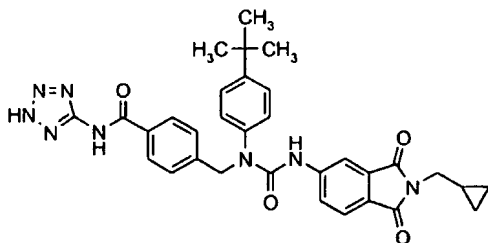


15 HPLC-MS (method B): m/z = 617.0, R_t = 7.48 min.

HPLC-MS (method B): m/z = 619.0, R_t = 7.73 min.

EXAMPLE 640

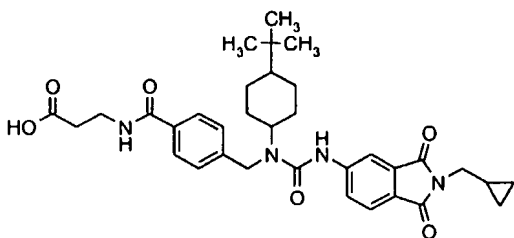
- 5 4-[1-(4-*tert*-Butylphenyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-*N*-(2H-tetrazol-5-yl)benzamide



HPLC-MS (method B): m/z = 593.0, R_t = 7.20 min.

- 10 **EXAMPLE 641**

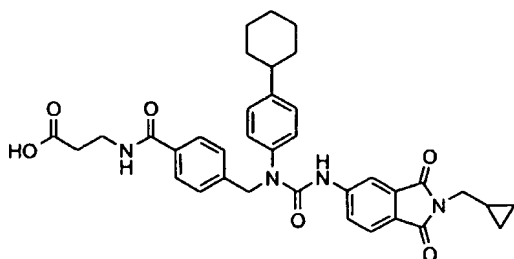
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-benzoylamino}propionic acid



- 15 HPLC-MS (method B): m/z = 603.0, R_t = 7.38 min.

EXAMPLE 642

3-{4-[3-(*N'*-[Cyclopropylmethyl]phthalimid-4-yl)-1-(4-cyclohexylphenyl)ureidomethyl]-benzoylamino}propionic acid

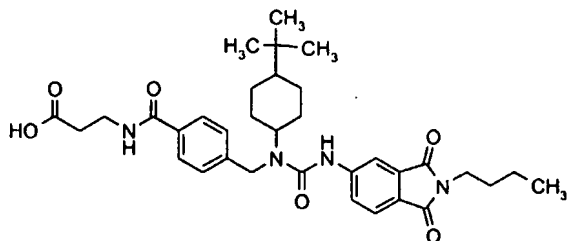


HPLC-MS (method B): m/z = 621.0, R_t = 7.92 min.

EXAMPLE 637

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-butylphthalimid-4-yl)ureidomethyl]benzoylamino}-
propionic acid

5

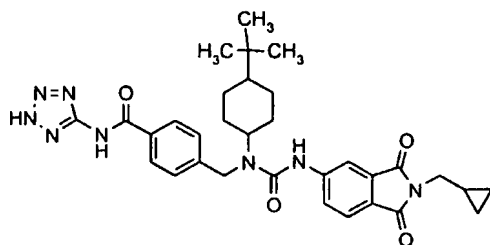


HPLC-MS (method B): m/z = 605.0, R_t = 7.58 min. (*cis*-isomer); R_t = 7.68 min. (*trans*-isomer).

EXAMPLE 638

4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-*N*-(2*H*-
tetrazol-5-yl)benzamide

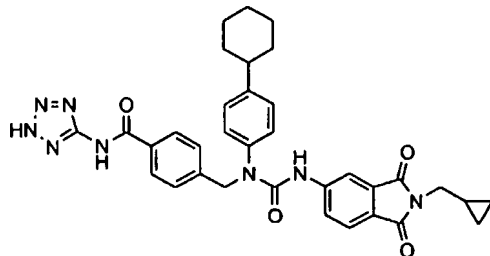
10



HPLC-MS (method B): m/z = 599.0, R_t = 7.52 min. (*cis*-isomer); R_t = 7.72 min. (*trans*-isomer).

EXAMPLE 639

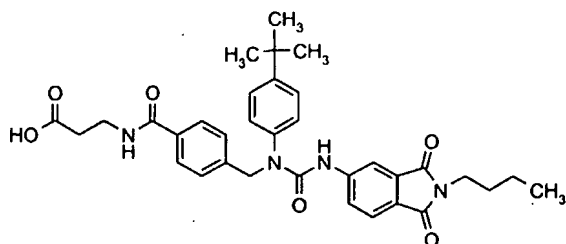
4-[1-(4-Cyclohexylphenyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-*N*-(2*H*-
tetrazol-5-yl)benzamide



20

EXAMPLE 634

3-{4-[3-(*N'*-Butylphthalimid-4-yl)-1-(4-*tert*-butylphenyl)ureidomethyl]benzoylamino}propionic acid

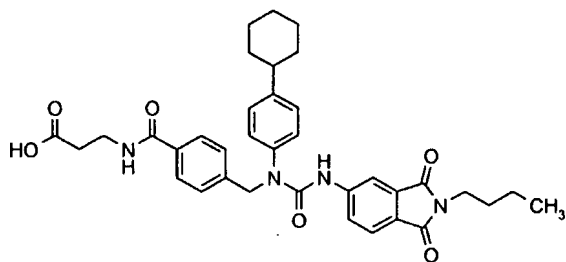


5

HPLC-MS (method B): m/z = 599.0, R_t = 7.15 min.

EXAMPLE 635

10 3-{4-[3-(*N'*-Butylphthalimid-4-yl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}propionic acid

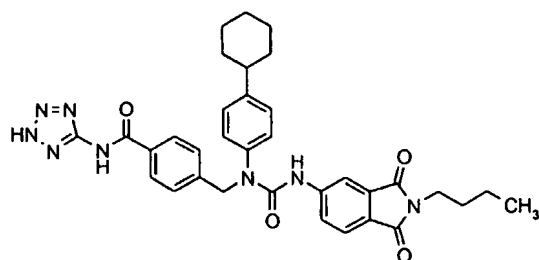


HPLC-MS (method B): m/z = 625.0, R_t = 7.68 min.

15

EXAMPLE 636

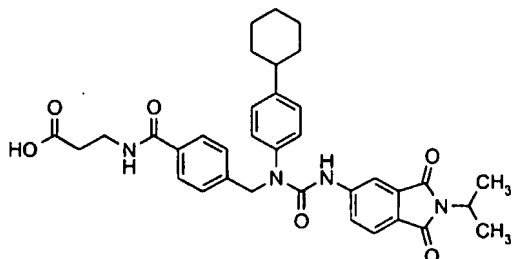
4-[3-(*N'*-Butylphthalimid-4-yl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



20

EXAMPLE 631

3-{4-[1-(4-Cyclohexyl-phenyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]benzoylamino}-propionic acid

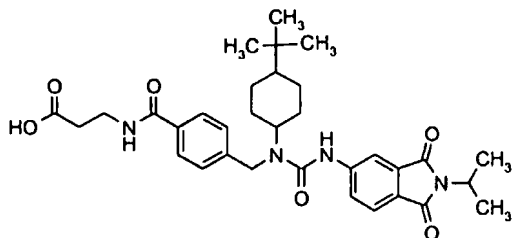


5

HPLC-MS (method B): m/z = 611.0, R_t = 7.42 min.

EXAMPLE 632

10 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]benzoylamino}-propionic acid

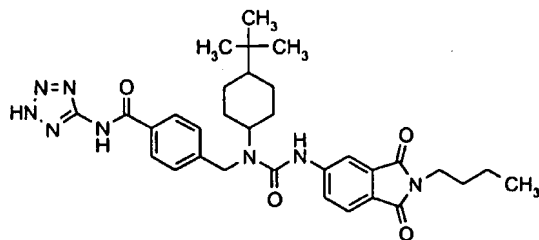


HPLC-MS (method B): m/z = 591.0, R_t = 7.35 min. (*cis*-isomer); R_t = 7.45 min. (*trans*-isomer).

15

EXAMPLE 633

4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-butylphthalimid-4-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

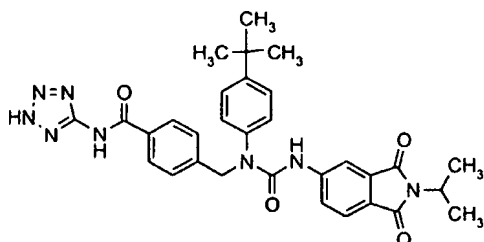


20

HPLC-MS (method B): m/z = 601.0, R_t = 7.68 min. (*cis*-isomer); R_t = 7.83 min. (*trans*-isomer).

EXAMPLE 628

4-[1-(4-*tert*-Butyl-phenyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

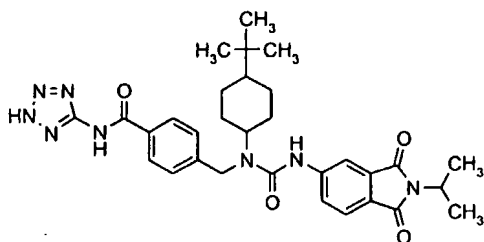


5

HPLC-MS (method B): m/z = 581.0, R_t = 7.62 min.

EXAMPLE 629

10 4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-isopropylphthalimid-5-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

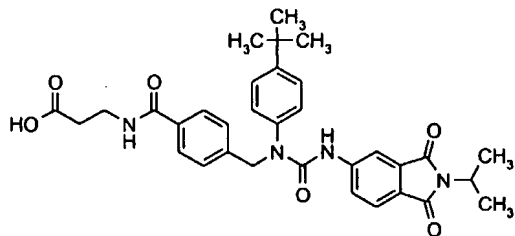


HPLC-MS (method B): m/z = 531.0, R_t = 7.52 min. (*cis*-isomer); R_t = 7.62 min. (*trans*-isomer).

15

EXAMPLE 630

3-{4-[1-(4-*tert*-Butylphenyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]benzoylamino}-propionic acid

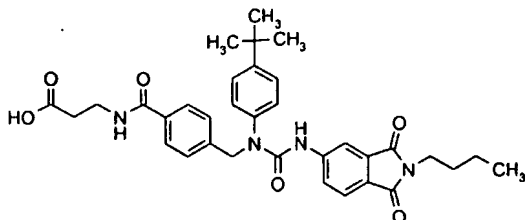


20

HPLC-MS (method B): m/z = 585.0, R_t = 6.83 min.

EXAMPLE 626

3-{4-[3-(*N*-Butylphthalimid-4-yl)-1-(4-*tert*-butylphenyl)ureidomethyl]benzoylamino}propionic acid



5

Prepared as described above using resin bound 3-{4-[(4-*tert*-butylphenylamino)methyl]-benzoylamino}propionic acid. An oil was obtained after TFA cleavage and evaporation of solvent. The oil was taken up in ethanol (3 mL) and added dropwise to water (25 mL) while stirring. A fine white powder was obtained which was collected by filtration and dried overnight in a vacuum oven to afford 231 mg (77%) of the title compound.

10

¹H NMR (DMSO-*d*₆): 0.89 ppm (t, 3H); 1.26 (s, 9H); 1.28 (m, 2H); 1.54 (m, 2H); 2.48 (m, 2H); 3.42 (m, 2H); 3.53 (t, 2H); 7.20 (d, 2H); 7.35 (d, 2H); 7.39 (d, 2H); 7.71 (d, 1H); 7.76 (d, 2H); 7.80 (dd, 1H); 8.03 (d, 1H); 8.47 (t, 1H); 8.95 (s, 1H); 12.25 (bs, 1H).

15

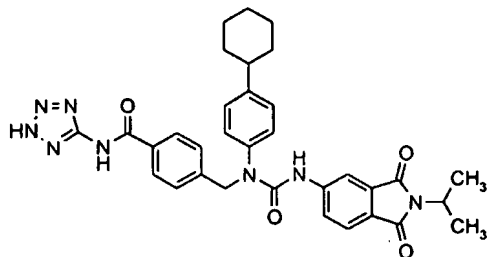
HPLC-MS (method B): *m/z* = 599, *R*_t = 7.15 min.

The following examples 627 to 645 were prepared in a similar way:

20

EXAMPLE 627

4-[1-(4-Cyclohexylphenyl)-3-(*N*-isopropylphthalimid-4-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



25

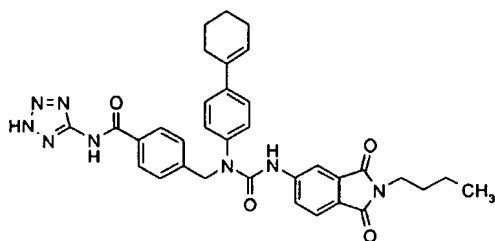
HPLC-MS (method B): *m/z* = 607.0, *R*_t = 7.62 min.

suspended in toluene (50 mL). Trichloromethyl chloroformate (22.0 mL, 180 mmol) was added and the suspension was heated to reflux. After 2 hours a clear solution was obtained. The solution was heated to reflux overnight. After cooling, solvent was removed and the residue was stripped twice with acetonitrile to remove traces of hydrochloric acid. The crystalline
5 residue (*N*-cyclopropylphthalimide-4-isocyanate) was sufficiently pure for further synthesis.

¹H NMR (CDCl₃): δ 1.10 ppm (m, 4H); 2.66 (m, 1H); 7.39 (d, 1H); 7.75 (d, 1H); 7.78 (dd, 1H).

EXAMPLE 625

10 4-[3-(*N*'-Butylphthalimid-4-yl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

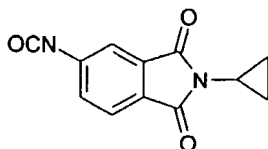


15 4-[(4-Cyclohex-1-enylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (0.5 mmol) assembled on 2-chlorotriyl resin (500 mg) as described under general procedure (Q) was treated with a solution of *N*-butylphthalimide-4-isocyanate (1220 mg, 5.0 mmol) in NMP/1,2-dichloropropane (1:5, 10 mL) for 48 hours. Solvent was drained and the resin was washed with DMF (3 x) and dichloromethane (10 x). Standard cleavage with 10% TFA/dichloromethane and evaporation of solvent afforded a powder, which was further purified by recrystallization from acetonitrile to afford 227 mg (73%) of the title compound.
20

¹H NMR (DMSO-*d*₆): δ 0.89 ppm (t, 3H); 1.28 (q, 2H); 1.57 (m, 4H); 1.72 (m, 2H); 2.17 (m, 2H); 2.45 (m, 2H); 3.54 (t, 2H); 5.04 (s, 2H); 6.20 (t, 1H); 7.25 (d, 2H); 7.41 (d, 2H); 7.48 (d, 2H); 7.72 (d, 1H); 7.84 (dd, 1H); 8.01 (d, 1H); 8.03 (d, 2H); 8.92 (s, 1H); 12.35 (s, 1H).

25

HPLC-MS (method B): *m/z* = 620, *R*_t = 5.15 min.

N-Cyclopropylphthalimide-4-isocyanate

Step 1: 4-Nitrophthalic anhydride (5.60 g, 28.9 mmol) was dissolved in THF (50 mL), and
5 cyclopropylamine (2.10 mL, 30 mmol) was added slowly while stirring under an inert atmosphere. After 30 min, a suspension was obtained. Triethylamine (8.2 mL, 60 mmol) and diisopropylcarbodiimide (5.50 mL, 35 mmol) were added followed by DMF (100 mL). The reaction mixture was then heated to 70°C for 48 hours. The mixture was cooled to room temperature and the reaction volume was reduced to one-tenth of the original volume by rotary evaporation
10 in in vacuo. The precipitated *N,N'*-diisopropylurea was removed by filtration, and water (40 mL) was added to the mother liquor resulting in formation of a precipitate. The precipitate was collected by filtration and dried overnight in a vacuum oven to give 6.02 g (90%) of *N*-cyclopropyl-4-nitrophthalimide.

15 ¹H NMR (DMSO-*d*₆): δ 0.92 ppm (m, 4H); 2.71 (s, 1H); 8.07 (d, 1H); 8.44 (d, 1H); 8.58 (dd, 1H).

HPLC-MS (method B): *m/z* = 233, *R*_t = 4.67 min.

20 Step 2: *N*-Cyclopropyl-4-nitrophthalimide (10.0 g, 43.0 mmol) was dissolved in ethanol (200 mL). Tin (II) chloride dihydrate (49.0 g, 215 mmol) was added, and the mixture was heated to reflux overnight. After cooling, the mixture was poured over crushed ice (1.0 L), and pH adjusted to 6.5 using 1 N NaOH. The mixture was passed through a small bed of celite, and the filtrate was subsequently extracted with ethyl acetate (1.2 L). The organic phase was dried
25 using anhydrous MgSO₄, and solvent was removed by rotary evaporation in vacuo, to afford crystalline *N*-cyclopropyl-4-aminophthalimide. Yield: 6.0 g (69%).

¹H NMR (DMSO-*d*₆): δ 0.85 ppm (m, 4H); 2.55 (m, 1H); 6.41 (bs, 2H); 6.77 (d, 1H); 6.86 (d, 1H); 7.44 (dd, 1H).

30

Step 3: *N*-Cyclopropyl-4-aminophthalimide (3.00 g, 15.0 mmol) was dissolved in THF (50 mL). A 3.5 N HCl – ethyl acetate solution (26 mL, 90.0 mmol) was added resulting in immediate precipitation of the hydrochloride salt. Solvent was removed, and the crystalline residue

evaporation. The residue was dried overnight in a vacuum oven to afford 6.49 g (82%) of pure *N*-cyclopropylmethyl-4-nitrophthalimide as a powder.

¹H NMR (DMSO-*d*₆): δ 0.36 ppm (d, 2H); 0.50 (d, 2H); 1.12 (m, 1H); 3.51 (d, 2H); 8.13 (d, 1H); 8.50 (s, 1H); 8.62 (d, 1H).

Step 2: *N*-Cyclopropylmethyl-4-nitrophthalimide (6.0 g, 24 mmol) in methanol (200 mL) was added dropwise over 30 min to a solution of sodium dithionite (27.0 g, 156 mmol) and sodium carbonate (13.0 g, 125 mmol) in water (200 mL) while the temperature was maintained at 70°C. The mixture was stirred at 70°C for an additional 50 min before it was allowed to cool to room temperature. The reaction volume was then reduced to one-third by rotary evaporation. Water (400 mL) was added, and the suspension extracted with ethyl acetate (2 x 450 mL). The combined organic solutions were dried with anhydrous MgSO₄. Solvent was then removed by rotary evaporation to afford 2.52 g (49%) of pure *N*-cyclopropylmethyl-4-aminophthalimide as a powder.

¹H NMR (DMSO-*d*₆): 0.25 ppm (d, 2H); 0.44 (d, 2H); 1.05 (m, 1H); 3.35 (d, 2H); 6.46 (s, 2H); 6.78 (d, 1H); 6.92 (s, 1H); 7.46 (d, 1H).

HPLC-MS (method B): *m/z* = 217, *R*_t = 4.65 min.

Step 3: *N*-Cyclopropylmethyl-4-aminophthalimide (2.5 g, 11.6 mmol) was suspended in toluene (30 mL) and bis(trichloromethyl) carbonate (2.28 g, 7.71 mmol) was added. The mixture was heated to reflux under an inert atmosphere for 2 hours. The reaction mixture was cooled on an ice bath before filtering. The filtrate was then taken to dryness, and the oily residue suspended in petroleum ether (40 mL). The pure title material was obtained as a precipitate, which was collected by filtration and washed twice with cold petroleum ether to afford 1.50 g (54%) of *N*-(cyclopropylmethyl)phthalimide-4-isocyanate.

¹H NMR (CDCl₃): δ 0.37 ppm (m, 2H); 0.50 (m, 2H); 1.19 (m, 1H); 3.54 (d, 2H); 7.89 (d, 1H); 7.54 (s, 1H); 7.81 (d, 1H).

trate was evaporated to dryness to afford a quantitative yield (8.70 g) of pure *N*-isopropyl-4-aminophthalimide.

^1H NMR (CDCl_3): δ 1.46 ppm (d, 6H); 4.47 (m, 1H); 6.82 (dd, 1H); 7.00 (d, 1H); 7.55 (d, 1H).

5

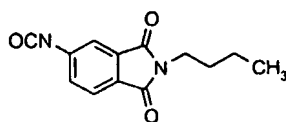
Step 3: *N*-Isopropyl-4-aminophthalimide (9.50 g, 47 mmol) was dissolved in THF (200 mL). While stirring, a solution of HCl in ethyl acetate (90 mL, 3.5 M, 315 mmol) was slowly added to form the anilinium hydrochloride. Solvent was removed, and the precipitate was re-suspended and evaporated twice from THF. The solid residue was then suspended in toluene (250 mL), and trichloromethyl chloroformate (60 mL, 500 mmol) was added. The suspension was heated to reflux and after 2 hours, a clear solution was obtained. Reflux was continued overnight. The solution was allowed to cool to room temperature before the solvent was removed by evaporation. The crystalline residue was stripped with toluene (2 x 200 mL) and acetonitrile (2 x 200 mL), and the obtained *N*-isopropylphthalimide-4-isocyanate was used for subsequent reactions without further purification. Yield : 10.7 g (99%).

10

15

^1H NMR (CDCl_3): δ 1.49 ppm (d, 6H); 4.50 (m, 1H); 7.37 (d, 1H); 7.51 (s, 1H); 7.76 (d, 1H).

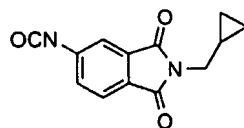
N-Butylphthalimide-4-isocyanate



20

This material was prepared similarly as described for *N*-isopropylphthalimide-4-isocyanate.

N-(Cyclopropylmethyl)phthalimide-4-isocyanate



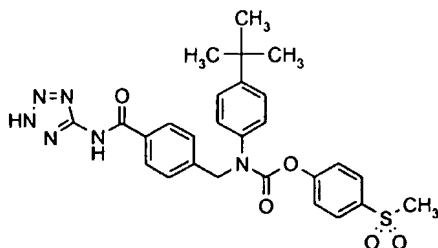
25

Step 1: 4-Nitrophthalimide (6.15 g, 32.0 mmol) was dissolved in DMF (60 mL). Cyclopropylmethyl bromide (9.3 mL, 96 mmol) and potassium carbonate (8.85 g, 64.0 mmol) were added and the mixture was heated to 100°C for 4 hours. The mixture was allowed to cool to room temperature, and then partitioned between water (500 mL) and ethyl acetate (400 mL). The organic phase was collected, dried with Na_2SO_4 , filtered and taken to dryness using rotary

30

EXAMPLE 624

(4-*tert*-Butylphenyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 4-(methylsulfonyl)-phenyl ester



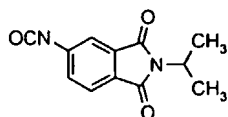
5

Prepared as described above in example 621. Yield: 15 mg.

HPLC-MS (method B): m/z = 549, R_t = 6.35 min.

- 10 Preparation of starting materials for phthalimide compounds of the invention:

N-Isopropylphthalimide-4-isocyanate



- 15 Step 1: 4-Nitroisophthalimide (25.0 g, 130.0 mmol) was dissolved in DMF (250 mL). Isopropyl bromide (61.0 mL, 650 mmol) and potassium carbonate (36.0 g, 260 mmol) were added and the mixture was heated to 60°C overnight. Water (1.0 L) was added, and the precipitate formed was collected by filtration, washed twice with water and dried overnight in a vacuum oven to afford 21.3 g (70%) of pure *N*-isopropyl-4-nitrophthalimide.

20

^1H NMR (DMSO- d_6): δ 1.42 ppm (d, 6H); 4.44 (m, 1H); 8.07 (d, 1H); 8.45 (s, 1H); 8.61 (d, 1H).

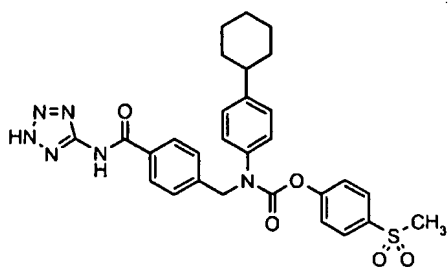
- 25 Step 2: *N*-Isopropyl-4-nitrophthalimide (10.0 g, 43.0 mmol) was dissolved in a mixture of THF (200 mL) and DMF (100 mL). 10% Palladium catalyst on carbon (1.0 g, 50% wet weight) was added and the mixture was hydrogenated in a low-pressure apparatus (1 atm.) overnight. The catalyst was then removed by filtering the mixture through a short pad of celite. The fil-

followed by dichloromethane (10 x). The product was cleaved from the support using 5% TFA in dichloromethane as described in general procedure (Q), and the pure product obtained as crystals after removal of solvent using speed vacuum. Yield: 5.0 mg.

- 5 HPLC-MS (method B): m/z = 579, R_t = 6.55 min.

EXAMPLE 622

(4-Cyclohexylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 4-(methylsulfonyl)-phenyl ester



10

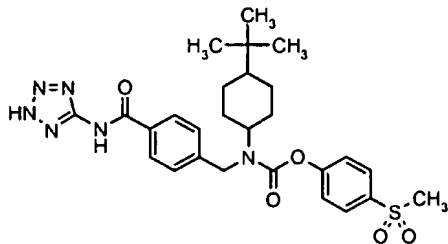
Prepared as described above in example 621. Yield: 15 mg.

HPLC-MS (method B): m/z = 575, R_t = 6.88 min.

15

EXAMPLE 623

(4-tert-Butylcyclohexyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 4-(methylsulfonyl)phenyl ester

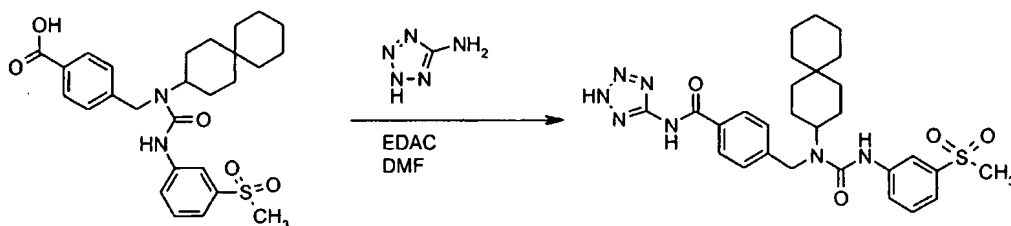


20

Prepared as described above in example 621. Yield: 15 mg.

HPLC-MS (method B): m/z = 555, R_t = 7.07 min.

481



4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

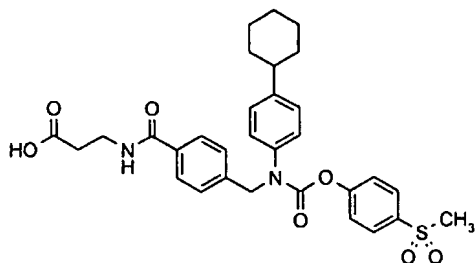
4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid (32.2 mg, 64.6 μ mol) was dissolved in DMF (1 mL) and added *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDAC) (16.5 mg, 86 μ mol) and 5-aminotetrazole·H₂O (16.5 mg, 160 μ mol). The mixture was stirred at 25°C for 1 day and concentrated *in vacuo*. Brine (5 mL) was added to the residue followed by a mixture of ethanol and chloroform (1:2, 10 mL). The phases were separated and the aqueous layer was extracted with a mixture of ethanol and chloroform (1:2, 2 x 10 mL). The combined organic extracts were dried over MgSO₄ and evaporated. The residue was purified by preparative HPLC affording the title compound.

¹H NMR (DMSO): δ 12.30 (s br, 1H); 8.80 (s, 1H); 8.11-8.02 (m, 3H); 7.85 (dt, 1H); 7.55-7.40 (m, 4H); 4.70 (s, 2H); 4.10 (m br 1H); 3.18 (s, 3H); 1.68-1.10 (m, 18H)

HPLC-MS (Method D): *m/z* = 566 (*M*+1). *R*_t = 3.03 min.

EXAMPLE 621

3-(4-[[[(4-Cyclohexylphenyl)-(4-(methylsulfonyl)phenoxy)carbonyl]amino]methyl]benzoylamino]propionic acid



20

3-(4-[[[(4-Cyclohexylphenyl)-(4-(methylsulfonyl)phenoxy)carbonyl]amino]methyl]benzoylamino]propionic acid (0.05 mmol) assembled on 2-chlorotrityl resin (50 mg) as described in general procedure (Q) was treated overnight with 3-chloroperbenzoic acid (34.5 mg, 0.200 mmol) in NMP (0.50 mL). The solvent was drained off, and the resin washed with DMF (3 x)

25

The above 4-(spiro[5.5]undec-3-ylaminomethyl)benzoic acid methyl ester (1.02 g, 3.2 mmol) was added acetonitrile (50 mL) and 3-(methylthio)phenylisocyanate (668 mg, 4 mmol). Upon stirring for 2 days, the reaction appeared incomplete as shown by HPLC, so another portion of 3-(methylthio)phenylisocyanate (240 mg) was added. After stirring for 2 hours the solvent was evaporated. The residue was taken up in dichloromethane (2 mL) and purified by chromatography on silica using dichloromethane as eluent affording 4-[3-(3-methylsulfanyl-phenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester (680 mg).



4-[3-(3-Methylsulfanyl-phenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]-benzoic acid methyl ester

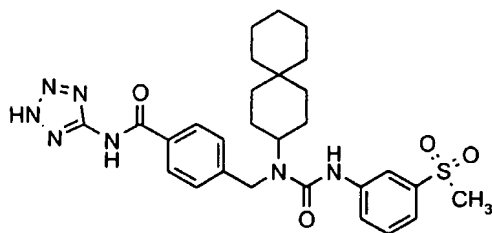
10

The above 4-[3-(3-methylsulfanylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester (550 mg, 1.14 mmol) was dissolved in 1,2-dichloroethane (10 mL) and added *m*-chloroperbenzoic acid (611 mg). The reaction was monitored by HPLC. Upon completion, dichloromethane (20 mL) was added to dissolve any precipitate formed during the reaction. Water (20 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (20 mL) and the combined organic phases were washed with saturated aqueous potassium carbonate (20 mL), water (20 mL) and brine (20 mL), dried over MgSO_4 and evaporated. The residue was purified on silica (150 g) using a mixture of heptane and ethyl acetate (1:1) as eluent affording 4-[3-(3-methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester (362 mg).

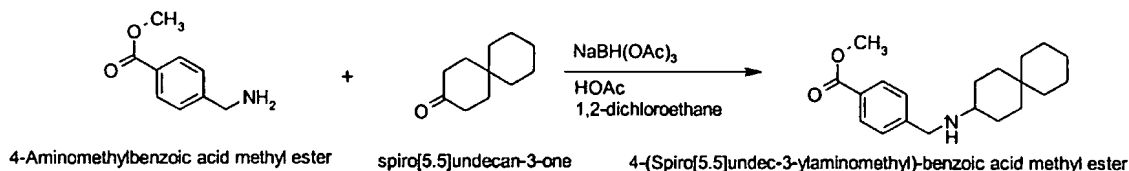
20

4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester was hydrolyzed to the corresponding carboxylic acid using 3 equiv. NaOH(aq) (4M) in dioxane.

25

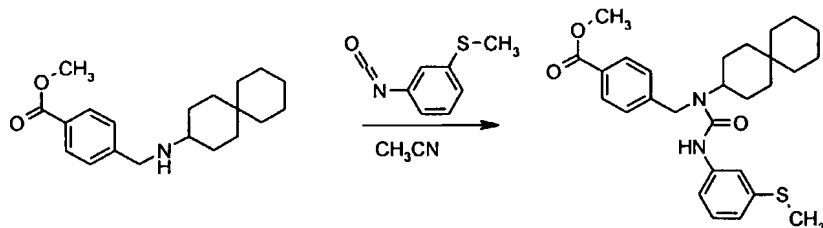
EXAMPLE 620**4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-ylureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide**

5



4-Aminomethylbenzoic acid methyl ester hydrochloride (1.45 g, 7.2 mmol) was suspended in 1,2-dichloroethane (50 mL) and added saturated aqueous potassium carbonate. The phases were separated and the aqueous layer was extracted with another portion of 1,2-dichloroethane (50 mL). The combined organic phases were added glacial acetic acid (435 μ L, 7.6 mmol) followed by spiro[5.5]undecan-3-one (1.2 g, 7.2 mmol). The suspension was stirred for 30 min at 25°C and sodium triacetoxyborohydride (2.27 g, 10.7 μ mol) was added. After stirring for 2 days at 25°C, water (100 mL) and saturated aqueous potassium carbonate (15 mL) were added. The phases were separated and the aqueous layer was extracted with 1,2-dichloroethane (2 x 100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried over MgSO_4 and evaporated to afford 4-(spiro[5.5]undec-3-ylaminomethyl)benzoic acid methyl ester which was used in the subsequent steps without further purification.

20

**4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]-benzoic acid methyl ester**

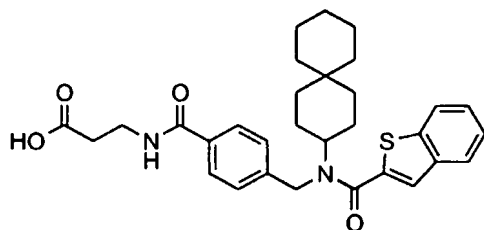
evaporated and water (10 mL) was added to the residue followed by saturated sodium bicarbonate (10 mL). The product was extracted using ethyl acetate (2 x 50 mL). The combined ethyl acetate extracts were washed with water (20 mL) and brine (20 mL). Drying the organic phases over MgSO_4 and evaporation of the solvent afforded 3-(4-((3-fluoro-5-trifluoromethylbenzoyl)spiro[5.5]undec-3-yl-amino)methyl)benzoylamino)propionic acid ethyl ester (295 mg) which was hydrolyzed using sodium hydroxide to afford the title compound.

^1H NMR (DMSO): δ 8.45 (t, 1H); 7.75-7.15 (m, 7H); 4.70+4.50 (s+s, 2H); 2.30 (t, 2H); 1.70-0.70 (m, 18-20H).

HPLC-MS (Method D): m/z = 563 ($M+1$). R_t = 3.46 min.

EXAMPLE 619

3-(4-(((Benzo[b]thiophene-2-carbonyl)spiro[5.5]undec-3-yl-amino)methyl)benzoylamino)-propionic acid



Prepared similarly as described in example 619.

^1H NMR (DMSO): δ 12.30 (s br, 1H); 8.51 (t, 1H); 8.05-7.55 (m, 5H); 7.50 (m 4H); 4.70 (s, 2H); 3.30 (s br, 2H); 1.80-0.90 (m, 18H).

HPLC-MS (Method D): m/z = 533 ($M+1$). R_t = 3.51 min.

The Benzo[b] thiophene-2-carbonyl chloride was prepared by adding toluene (2 mL), DMF (2 drops) and thionyl chloride (50 μL) to benzo[b]thiophene-2-carboxylic acid. Heating the mixture to reflux for 5 hours followed by removal of the solvent afforded the crude product, which was used without further purification.

below 35°C. After all the bromine had been added the mixture was stirred for 16 hours and then filtered and the residue washed with water. The combined filtrate and the washings were neutralized with concentrated aqueous ammonia. The precipitate was collected on a filter, dried and recrystallized from toluene/hexane to yield 6,7-(tetrafluoroethylenedioxy)-
 5 benzothiazol-2-ylamine.

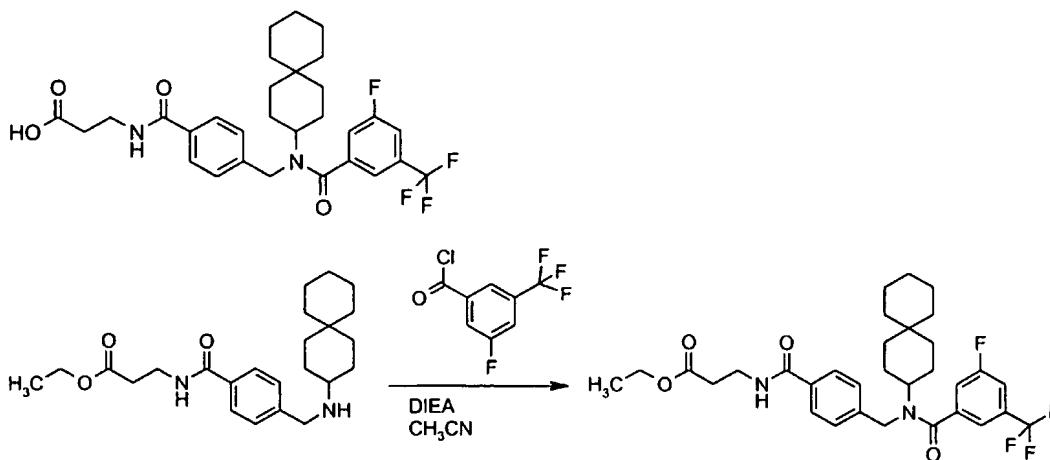
The above 6,7-(tetrafluoroethylenedioxy)benzothiazol-2-ylamine was converted to the title compound using a similar method as described above.

10 ¹H NMR (CDCl₃): δ 5.5 (2H, br s), 7.30 (1H, s), 7.37, (1H, s).

HPLC-MS (Method B): R_t = 8.72 min, m/z = 683 (M + 1).

EXAMPLE 618

15 3-(4-((3-Fluoro-5-trifluoromethylbenzoyl)spiro[5.5]undec-3-yl-amino)methyl)benzoylamino)-propionic acid

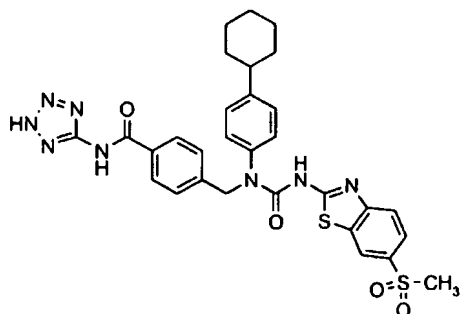


3-[4-(Spiro[5.5]undec-3-ylaminomethyl)benzoylamino]propionic acid ethyl ester

20 3-[4-(Spiro[5.5]undec-3-ylaminomethyl)benzoylamino]propionic acid ethyl ester was prepared by reductive alkylation of 3-(4-aminomethyl-benzoylamino)propionic acid ethyl ester with spiro[5.5]undecan-3-one. 3-[4-(Spiro[5.5]undec-3-ylaminomethyl)benzoylamino]propionic acid ethyl ester (200 mg, 499 μmol) was dissolved in acetonitrile (5 mL) and diisopropylethyl-
 25 amine (170 μL) and cooled on an ice bath. Commercially available 3-fluoro-5-(trifluoro-methyl)benzoylchloride (136 mg, 602 μmol) dissolved in acetonitrile (5 mL) was added drop-wise. The reaction was complete within one hour as shown by HPLC. The solvent was

EXAMPLE 616

4-[1-(4-Cyclohexylphenyl)-3-(6-methylsulfonylbenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

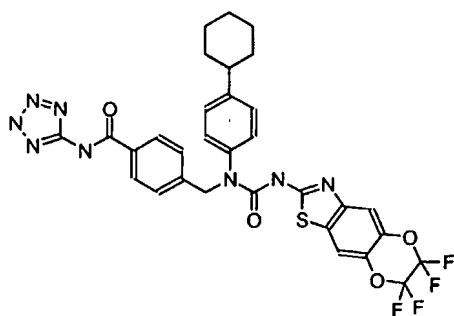
The title compound was made similarly as described in example 341.

HPLC-MS (Method C): $R_t = 5.07$ min, $m/z = 631$ (M+1).

10

EXAMPLE 617

4-[1-(4-Cyclohexylphenyl)-3-(6,7-(tetrafluoroethylenedioxy)benzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



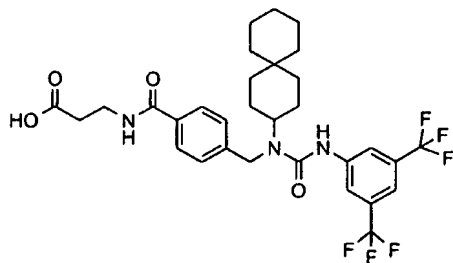
15

6,7-(Tetrafluoroethylenedioxy)benzothiazol-2-ylamine was prepared from 6-amino-2,2,3,3-tetrafluoro-1,4-benzodioxene using the general procedure described in Stuckwisch C. G. *J. Am. Chem. Soc.* **1949** 71, 3417:

20 To a suspension of 6-amino-2,2,3,3-tetrafluoro-1,4-benzodioxene (2 g, 9 mmol) and sodium thiocyanate (3.5 g, 43 mmol) in acetic acid (16 mL) was added dropwise, with stirring, bromine (1.4 g, 9 mmol) dissolved in acetic acid (7 mL) while the temperature was kept

EXAMPLE 614

3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-spiro[5.5]undec-3-ylureidomethyl]benzoylamino}-propionic acid



5

The title compound was made similarly as described in example 89.

^1H NMR (DMSO): δ 12.20 (s br, 1H); 9.05 (s, 1H); 8.48 (t, 1H); 8.22 (s, 2H); 7.72 (d, 2H); 7.55 (s, 1H); 7.32 (d, 2H); 4.65 (s, 2H); 4.08 (t br, 1H); 3.48 (q, 2H); 1.70-1.05 (m, 18H)

10

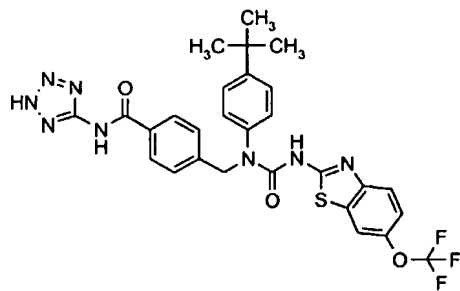
HPLC-MS (Method B): m/z = 628 ($M+1$). R_t = 8.30 min.

Spiro[5.5]undecan-3-one was prepared as described by Rice *et al*, *J. Org. Chem.*, **26**, 2637-2640, (1964).

15

EXAMPLE 615

4-[1-(4-*tert*-Butylphenyl)-3-(6-trifluoromethoxybenzothiazol-2-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



20

The title compound was made similarly as described in example 341.

^1H NMR (DMSO- d_6): δ 1.30 (9H, s), 5.14 (2H, s), 7.20-7.42, (7H, m), 7.48 (2H, d), 7.98, (1H, s), 8.08 (2H, d), 12.40 (1H, s).

After stirring for 2 hours at room temperature, the mixture was diluted with water, and extracted with diethyl ether. The combined organic extracts were dried (MgSO_4), and concentrated to give 3-methylsulfonyl benzyl alcohol (3.5g, 93%).

- 5 ^1H NMR (CDCl_3) δ : 3.02 (s, 3H), 4.68 (s, 2H), 7.47 (t, 1H), 7.57 (d, 1H), 7.75 (d, 1H), 7.89 (s, 1H).

To a solution of 3-methylsulfonyl benzyl alcohol (3.5 g, 28.6 mmol) in dichloromethane (50 mL) was added pyridinium chloro chromate (PCC) (9.1 g, 42.2 mmol). The mixture was
10 stirred at room temperature for 3 hours. After workup and column chromatography on silica gel eluting with hexane:ethyl acetate, 1:1, 3-methylsulfonylbenzaldehyde was obtained as white solid.

- ^1H NMR (CDCl_3) δ : 3.09 (s, 3H), 7.75 (t, 1H), 8.10-8.21 (2d, 2H), 8.40 (s, 1H), 10.11 (s, 1H).
15

To a solution of 3-methylsulfonylbenzaldehyde (0.93 g, 5.1 mmol) and ethyl 3-({[4-(*tert*-butyl)-cyclohexyl]amino}methyl)benzoyl]amino}propanoate (1.9 g, 5.1 mmol) in dry DMF (50 mL) was added sodium triacetoxy borohydride (1.6 g, 7.5 mmol) and a catalytic amount of trifluoroacetic acid. The mixture was diluted with water and extracted with ethyl acetate. The
20 combined organic extracts were dried (MgSO_4), and concentrated. The residue was dissolved in methanol, and saponified by 2M LiOH aqueous solution. After the reaction was complete, the mixture was acidified by 2M HCl, diluted with water, and extracted with ethyl acetate. The combined organic extracts were dried (MgSO_4), and concentrated. The residue was purified by HPLC to give the title compound.

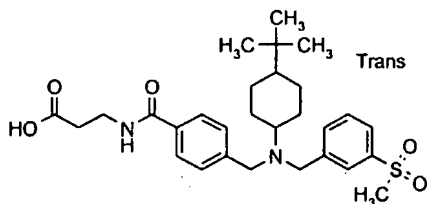
- 25 ^1H NMR (CDCl_3) δ : 0.78 (s, 9H), 0.81-0.96 (br, 3H), 1.18-1.39 (br, 2H), 1.71-1.98 (m, 4H), 2.40 (t, 1H), 2.56 (br, 2H), 3.53 (m, 6H), 7.25-7.86 (m, 8H).

- LC-MS (APCI, pos.): 529(M+1).
30

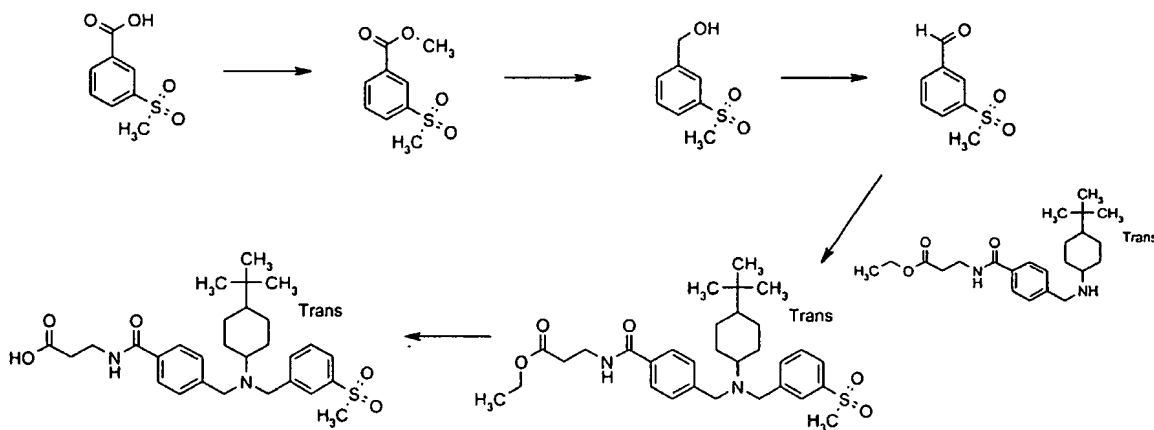
MS (APCI, pos.): 565.1.

EXAMPLE 613

3-(4-[[*(trans*-4-*tert*-Butylcyclohexyl)-(3-methylsulfonylbenzyl)amino]methyl]benzoylamino)-
propionic acid



Reaction scheme:



To a solution of 3-methylsulfonylbenzoic acid (10 g, 50 mmol) in anhydrous methanol (100 mL) was added conc. sulfuric acid (10 mL). The mixture was refluxed for 4 hours and then concentrated to one-third volume. Water (200 mL) was added, and the mixture was extracted with diethyl ether. The organic extract was washed with 10% sodium carbonate solution, and dried over Na₂SO₄. After concentration, 8.6 g (81%) of methyl 3-methylsulfonylbenzoate was obtained.

¹H NMR (CDCl₃) δ: 3.11 (s, 3H), 4.02 (s, 3H), 7.68 (t, 1H), 8.13 (d, 1H), 8.32 (d, 1H), 6.00 (s, 1H).

To a solution of methyl 3-methylsulfonylbenzoate (4.4 g, 20.3 mmol) in anhydrous THF (100 mL) was added lithium aluminum hydride (7 mL, 1.0 M solution in THF) via syringe at 0°C.

To solution of ethyl 3-{{(6-chloromethyl-3-pyridinyl)carbonyl}aminopropanoate (4.0 g, 14.8 mmol) in DMSO (40 mL) was added KH_2PO_4 (2.6 g, 14.8 mmol), K_2HPO_4 (1.0 g, 7.4 mmol) and sodium bromide (1.5 g, 14.8 mmol). The mixture was heated at 100 °C under nitrogen for 6 hours. TLC showed the starting material was completely consumed. The mixture was
5 poured onto water (100 mL), and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried (MgSO_4), and concentrated. This material (aldehyde) was used without further purification in the next step.

The crude material (283 mg) was dissolved in dichloromethane (10 mL), and *tert*-butylcyclo-
10 hexylamine (70 mg, 0.45 mmol) and sodium triacetoxy borohydride (190 mg, 0.89 mmol) were added. The mixture was stirred at room temperature for 16 hours, diluted with dichloromethane (20 mL), washed with sodium bicarbonate solution (20 mL), brine (20 mL), dried (MgSO_4), and concentrated. Flash chromatography on silicagel eluting with chloroform:-methanol:ammonia:water, 90:10:0.5:0.5 provided the desired secondary amine (190 mg); MS
15 (APCI, pos.): 390.2.

This material was dissolved in chloroform (5 mL), and 4-trifluoromethoxyphenyl isocyanate (150 mg, 0.73 mmol) was added. After stirring at room temperature for 16 hours, the mixture was concentrated. Flash chromatography on silica gel eluting with hexane:ethyl acetate, 1:1
20 afforded the ethyl ester of the title compound (225 mg).

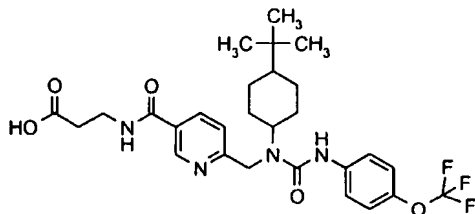
^1H NMR (CDCl_3): δ 0.84 (s, 9H), 0.91-1.84 (m, 9H), 1.27 (t, 3H), 2.66 (t, 2H), 3.74 (q, 2H), 4.12 (m, 1H), 4.17 (q, 2H), 4.48 (s, 2H), 7.07 (t, 1H), 7.12 (d, 2H), 7.41 (d, 1H), 7.46 (d, 2H), 8.13 (d, 1H), 8.98 (d, 1H), 9.54 (s, 1H), 9.75 (s, 1H).

25

The above material was dissolved in THF (5 mL), and 1M LiOH (1 mL) was added. After stirring at room temperature for 3 hours, the solution was acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in chloroform (20 mL), washed with brine (10 mL), dried (MgSO_4) and concentrated. The title compound crystallized from dichloromethane on
30 addition of hexane.

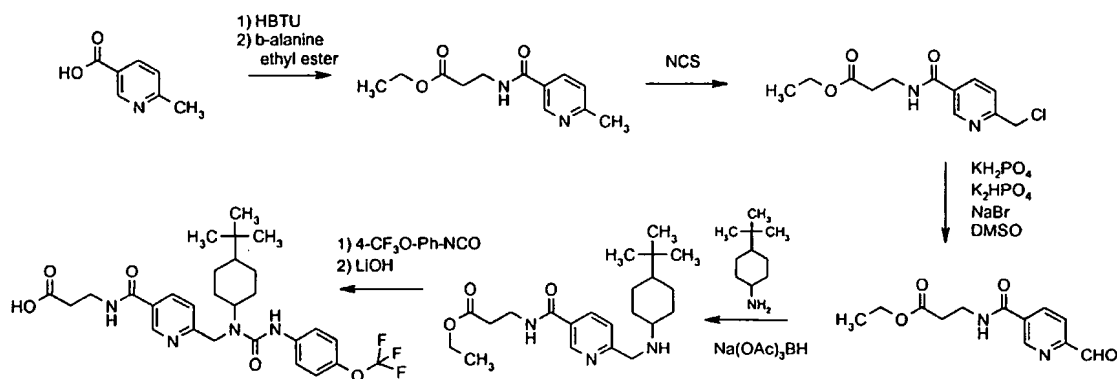
35

^1H NMR ($\text{DMSO}-d_6$): δ 0.82 (s, 9H), 0.93-1.75 (m, 9H), 2.50 (t, 2H), 3.43 (t, 2H), 4.63 (m, 1H), 4.63 (s, 2H), 7.24 (d, 2H), 7.38 (d, 1H), 7.55 (d, 2H), 8.13 (d, 1H), 8.73 (t, 1H), 8.93 (s, 1H), 9.05 (s, 1H).

EXAMPLE 612**3-({6-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]pyridine-3-carbonyl}amino)propionic acid**

5

Reaction scheme:



- 10 To solution of 6-methylnicotinic acid (4.9 g, 35.7 mmol) in DMF (50 mL) was added HBTU (16.2 g, 42.8 mmol) and diisopropylethylamine (11.0 g, 85 mmol). The mixture was stirred at 0°C for 30 min, and β-alanine ethyl ester hydrochloride (6.57 g, 42.8 mmol) was added at 0°C. The reaction was monitored by TLC. The reaction mixture was concentrated in vacuo, and the residue was dissolved in carbon tetrachloride (200 mL). NCS (5.2 g, 38.9 mmol) and a catalytic amount of benzoyl peroxide were added. After refluxing for 2 hours, the solvent was removed in vacuo. Column chromatography on silica gel eluting with hexane/ethyl acetate, 1:1 provided ethyl 3-((6-chloromethyl-3-pyridinyl)carbonyl)aminopropionate as a white solid (2.9 g, overall yield 30%)
- 15
- 20 ¹H NMR (CDCl₃): δ: 1.20 (t, 3H), 2.55 (t, 2H), 3.70 (q, 2H), 4.13 (q, 2H), 4.68 (s, 2H), 7.52 (d, 1H), 7.57 (t, 1H), 8.15 (d, 1H), 8.94 (s, 1H).

GC-MS (pos.): 255, 181.

N-{4-[[[3-(2-ethoxy-1,1-dimethyl-2-oxoethyl)cyclohexyl][4-(trifluoromethoxy)anilino]carbonyl]-
5 amino)methyl]benzoylamino}propionic acid

To a solution of ethyl 2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-2-methylpropanoate (694 mg, 3.51 mmol) in THF (5 mL) was added 1N HCl. The mixture was stirred at room temperature for 72 hours, diluted with sodium bicarbonate solution (20 mL), and extracted with ether (3 x 30
10 mL). The combined organic extracts were dried (MgSO₄), and concentrated to give 666 mg colourless oil, GC-MS (pos.) 211, 138. The material was dissolved in ethanol (5 mL), and 20 mg Pd/C (10% Pd) was added. The mixture was stirred under a hydrogen atmosphere for 16 hours. The catalyst was filtered off by suction through celite, and the filtrate was concentrated to give 670 mg colorless oil. This material was dissolved in DMF (10 mL), and THF (10
15 mL), and *N*-[4-(aminomethyl)benzoylamino]propionic acid (700 mg, 3.14mmol) was added followed by sodium triacetoxo borohydride (1.0 g, 4.7 mmol). The mixture was stirred at room temperature for five days, and filtered by suction. The filtrate was concentrated, and coevaporated with methanol and dichloromethane. The residue was dissolved in dichloromethane (5 mL), and triethylamine (1 mL) and 4-trifluoromethoxyphenyl isocyanate (650 mg,
20 3.20 mmol) was added. After stirring for 16h at room temperature, the mixture was filtered by suction, and the filtrate was concentrated. The residue was dissolved in dichloromethane (100 mL), washed with 1N HCl (2 x 50 mL), brine (50 mL), dried (MgSO₄), and concentrated. Flash chromatography on silicagel eluting with chloroform/methanol, 9:1 provided the title compound.

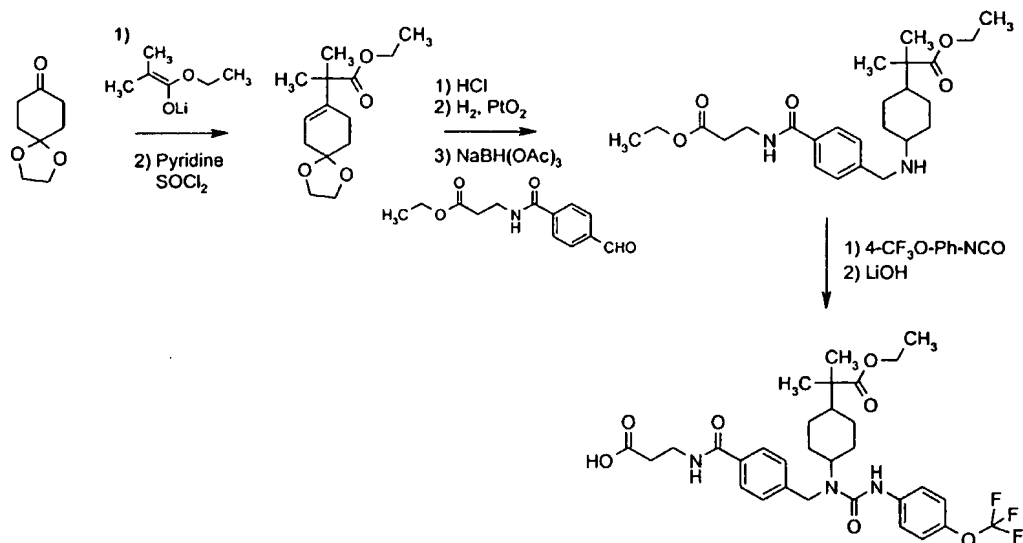
25

¹H NMR (CD₃OD): δ 1.06 (s, 1H), 1.09 (s, 6H), 1.22 (t, 2H), 1.46-1.85 (m, 8H), 2.69 (t, 2H), 3.60 (t, 2H), 4.03 – 4.15 (m, 2H), 4.07 (s, 2H), 7.14 (d, 2H), 7.34–7.41 (m, 4H), 7.77 (d, 2H).

MS (APCI, pos.): 622.2

30

Reaction scheme:



Ethyl 2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-2-methylpropanoate:

5

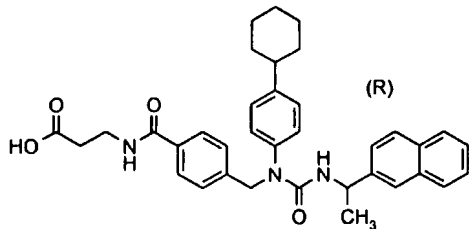
To a solution of diisopropylamine (10.1g, 0.1mol) in THF (50 mL) at -78°C was added n-butyllithium (48 mL of a 2M solution in hexane) during a period of 15 min. After 15 min ethyl isobutyrate (11.6 g, 0.1mol) was added dropwise during a period of 15 min. After additional 15 min at -78°C, a precooled solution of 1,4-cyclohexanedione monoethylene ketal in THF (80 mL) was added *via cannula* during a period of 15 min. After stirring for 2 hours at -78°C, the mixture was allowed to reach room temperature. It was poured onto ammonium chloride solution (100 mL), and extracted with ether (3 x 50 mL). The combined organic extracts were dried (MgSO_4) and concentrated to give 22 g colorless oil; GC-MS (pos.): 273, 255, 181.

15 The crude material was dissolved in pyridine (80 mL), and thionyl chloride (7.5 mL) was added dropwise with cooling in an ice bath. After stirring for 16 hours at room temperature, water (100 mL), and ether (300 mL) was added. The two layers were separated, the organic layer was washed with 1N HCl (3 x 50 mL), brine (2 x 50 mL), dried (MgSO₄), and concentrated to give 18.3 g of ethyl 2-(1,4-dioxaspiro[4,5]dec-7-en-8-yl)-2-methylpropanoate as a
20 colourless oil.

¹H NMR (CDCl₃): δ 1.22 (t, 3H), 1.30 (s, 6H), 1.74 (t, 2H), 2.18 (m, 2H), 2.33 (s, 2H), 3.96 (m, 4H), 4.13 (q, 2H), 5.50 (s, 1H).

Example 610 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-[(1R)-1-(2-naphthyl)ethyl]ureidomethyl]benzoylamino}-propionic acid



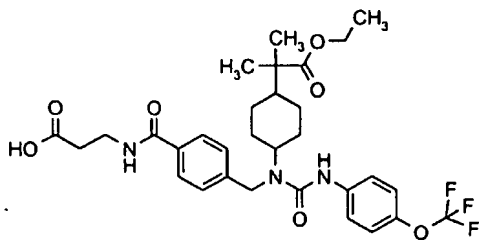
5

¹H NMR (DMSO-*d*₆): δ 1.15-1.86 (m, 14H), 2.50 (t, 2H), 3.44 (q, 2H), 4.87 (s, 2H), 5.06 (t, 1H), 6.26 (d, 2H), 7.10 (d, 2H), 7.19 (d, 2H), 7.26 (d, 2H), 7.43-7.50 (m, 3H), 7.68-7.76 (m, 3H), 7.80-7.91 (m, 3H), 8.44 (s, 1H), 12.13 (s, 1H).

10 LC-MS (APCI, pos.): 578 (M+1).

EXAMPLE 611

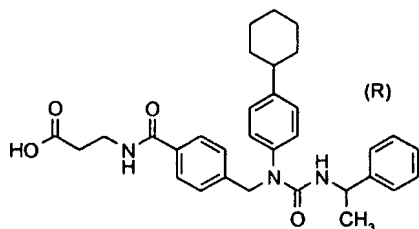
2-{4-[1-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(4-trifluoromethoxyphenyl)ureido]cyclohexyl}-2-methylpropionic acid ethyl ester



15

Example 608 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-((1R)-1-phenylethyl)ureidomethyl]benzoylamino}propionic acid



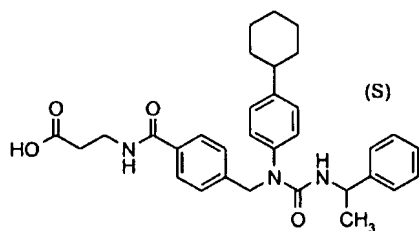
5

^1H NMR (acetone- d_6): δ 1.18-1.48 (m, 9H), 1.68-1.90 (m, 4), 2.51 (m, 1H), 2.65 (t, 2H), 3.63 (q, 2H), 4.91 (s, 2H), 5.03 (m, 1H), 5.28 (d, 1H), 7.08-7.35 (m, 11H), 7.70-7.82 (m, 3H), 10.7 (br, 1H).

10 LC-MS (APCI, pos.): 528 (M+1).

Example 609 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-((1S)-1-phenylethyl)ureidomethyl]benzoylamino}propionic acid



15

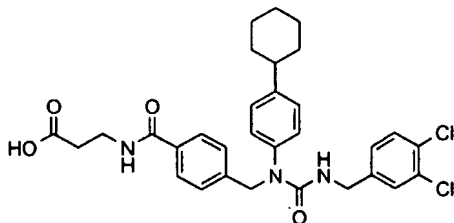
^1H NMR (DMSO- d_6): δ 1.12-1.40 (m, 9H), 1.62-1.85 (m, 5H), 2.50 (t, 2H), 3.43 (q, 2H), 4.78-4.95 (m, 3H), 6.09 (d, 2H), 7.07 (d, 2H), 7.14-7.34 (m, 9H), 7.73 (d, 2H), 8.44 (s, 1H), 12.15 (s, 1H).

20

LC-MS: (APCI, pos.): 528 (M+1).

Example 606 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorobenzyl)ureidomethyl]benzoylamino}propionic acid



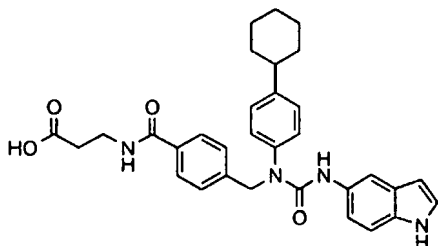
5

^1H NMR (DMSO- d_6): δ 1.15 (m, 1H), 1.34 (t, 4H), 1.70 (m, 1H), 1.75 (d, 4H), 2.45 (t, 2H), 3.45 (qt, 2H), 4.20 (d, 2H), 4.84 (s, 2H), 6.56 (t, 1H), 7.08 (d, 2H), 7.19-7.27 (m, 5H), 7.45 (s, 1H), 7.57 (d, 1H), 7.73 (d, 2H), 8.48 (t, 1H), 12.21 (s, 1H).

10 MS (APCI, pos): 582.1, 583.1, 584.1

Example 607 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-(1H-indol-5-yl)ureidomethyl]benzoylamino}propionic acid



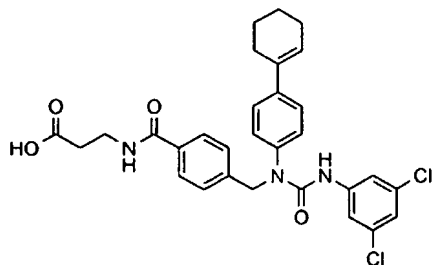
15

^1H NMR (DMSO- d_6): δ : 1.12-1.45 (m, 5H), 1.63-1.87 (m, 5H), 2.40-2.55 (br, 2H), 3.43 (q, 2H), 4.96 (s, 2H), 6.32 (s, 1H), 7.0-7.08 (q, 1H), 7.13-7.29 (m, 6H), 7.36 (d, 2H), 7.54 (s, 1H), 7.76 (m, 3H), 8.48 (t, 1H), 10.9 (s, 1H).

20 LC-MS (APCI, pos.): 539 (M+1).

Example 605 (General procedure (Z))

3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid



5

Steps A to C of this general procedure (Z) are similar to steps A to C of the general procedure (Y).

Step D: To a solution of the above benzoic acid (0.4 g, 0.81 mmol, prepared in step C) in DMF (4 mL) were added HBTU (0.37 g, 0.90 mmol), diisopropylethylamine (0.30 g, 2.4 mmol), and ethyl 3-aminopropanoate hydrochloride (0.30 g, 2.4 mmol). After stirring the solution for 16 hours, the reaction was diluted with ethyl acetate and washed with 1N HCl (3x), brine (3x), dried over MgSO₄, filtered, and concentrated to a syrup. The crude material was introduced into a silica gel column and eluted with ethyl acetate/hexane (1/3 to 4/6) to afford 3-{4-[1-(4-cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid ethyl ester in quantitative yield.

Step E: The propionic acid ethyl ester prepared in step D was dissolved in THF (6 mL) and MeOH (3 mL). A solution of 2 M LiOH (3 mL) was then added and the reaction was stirred at room temperature for 30 minutes. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1 N HCl (2x), brine (2x), dried over MgSO₄, filtered, and concentrated to a syrup. Addition of hexane followed by trituration precipitated the title compound (270 mg, 0.48 mmol) as a cream colored solid.

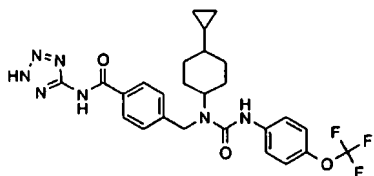
¹H NMR (acetone-*d*₆): δ: 1.58-1.85 (m, 4H), 2.15-2.28 (m, 2H), 2.32-2.44 (m, 2H), 2.65 (t, 2H), 3.63 (q, 2H), 5.01 (s, 2H), 6.24 (m, 1H), 7.04 (m, 1H), 7.22 (d, 2H), 7.38-7.48 (m, 4H), 7.61 (d, 2H), 7.70-7.88 (m, 4H), 10.7 (br, 1H).

LC-MS (APCI, pos.): 567(M+1).

^1H NMR ($\text{DMSO}-d_6$): δ 0.83 (9H,s), 1.20 (1H,m), 1.35 (2H,m), 1.55 (4H,m), 1.77 (2H,m), 4.31 (1H,m), 4.76 (2H,s), 7.42 (2H,d), 7.61 (1H,s), 8.05 (2H,d), 8.26 (2H, s), 9.12 (1H, s), 12.32 (1H,s).

5 **EXAMPLE 604**

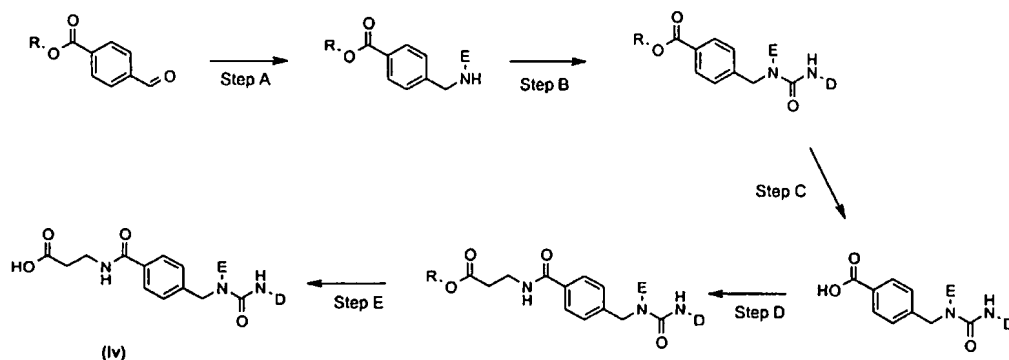
4-[1-(4-Cyclopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10 ^1H NMR ($\text{DMSO}-d_6$): δ 12.2 (s, broad), 8.59 (1H, s), 8.03 (2H, d), 7.55 (2H, d), 7.42 (2H, d), 7.22 (2H, d), 4.63 (2H, broad), 4.12 (1H, m), 1.80-1.00 (9H, m), 0.49 (2H, m), 0.35 (2H, m).

HPLC-MS (method B): m/z : 544, R_t = 7.70 min.

15 General procedure (Z) for solution phase preparation of compounds of general formula (iv):



wherein

20

E and D are as defined for formula (I) and

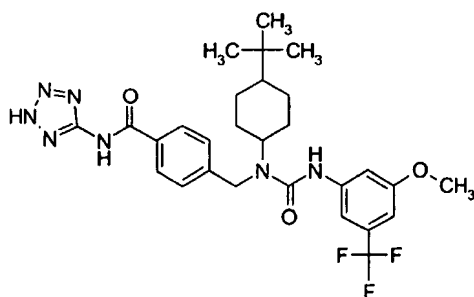
R is C_{1-6} -alkyl.

54.25% C; 4.02% H; 15.16% N.

EXAMPLE 602 (general procedure (Y))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

5



HPLC-MS (method B): m/z : 574, R_t = 7.85 min.

- 10 ^1H NMR ($\text{DMSO}-d_6$): δ 0.83 (9H,s), 0.96 (1H,m), 1.14 (2H,m), 1.44 (2H,m), 1.73 (4H,m), 3.80 (3H, s), 4.08 (1H,m), 4.68 (2H,s), 6.82 (1H,s), 7.42 (2H,d), 7.46 (1H,s), 7.53 (1H,s), 8.05 (2H,d), 8.71 (1H,s), 12.36 (1H,s).

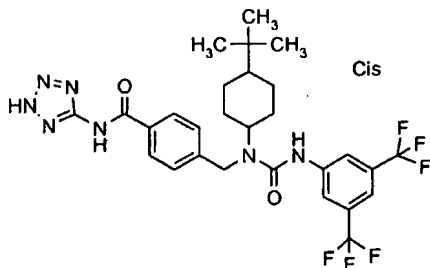
Microanalysis: calculated for $\text{C}_{28}\text{H}_{34}\text{F}_3\text{N}_7\text{O}_3$:

- 15 58.63% C; 5.97% H; 17.09% N; Found:
58.45% C; 6.29% H; 17.04% N.

EXAMPLE 603 (general procedure (Y))

4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(*cis*-4-*tert*-butylcyclohexyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

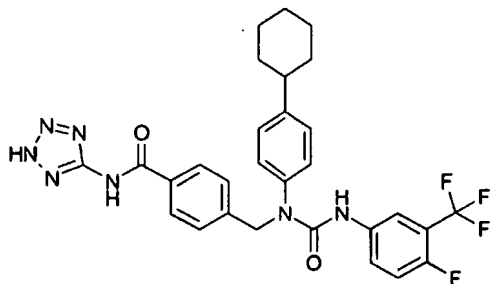
20



HPLC-MS (method B): m/z : 512, R_t = 8.20 min.

EXAMPLE 600 (general procedure (Y))

4-[1-(4-Cyclohexylphenyl)-3-(4-fluoro-3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

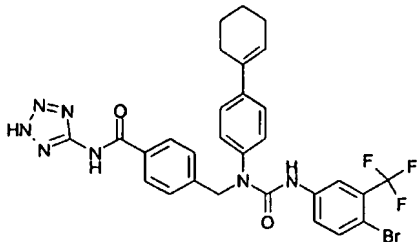
HPLC-MS (method B): m/z: 582. R_t = 7.75 min.

^1H NMR (DMSO- d_6): δ 1.20-1.45 (5H, m), 1.65-1.85 (5H, m), 5.00 (2H, s), 7.22 (4H, m), 7.38 (1H, t), 7.48 (2H, d), 7.80 (1H, broad), 7.92 (1H, d), 8.03 (2H, d), 8.62 (1H, s), 12.4 (1H, broad).

10

EXAMPLE 601 (general procedure (Y))

4-[3-(4-Bromo-3-trifluoromethylphenyl)-1-(4-cyclohex-1-enyl)phenyl]ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

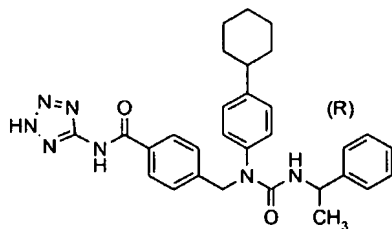
HPLC-MS (method B): m/z: 641, R_t = 8.2 min.

^1H NMR (DMSO- d_6): δ 1.55-1.65 (m, 2H), 1.67-1.77 (m, 2H), 2.19 (broad, 2H), 2.35 (broad, 2H), 5.00 (s, 2H), 6.20 (s, 1H), 7.23 (d, 2H), 7.45 (dd, 4H), 7.72 (d, 1H), 7.75 (d, 1H), 8.04 (d, 2H), 8.05 (s, 1H), 8.72 (s, 1H), 12.4 (broad, 1H).

20

Microanalysis: calculated for $\text{C}_{29}\text{H}_{25}\text{BrF}_3\text{N}_7\text{O}_2$:

54.39% C; 3.93% H; 15.31% N. Found:

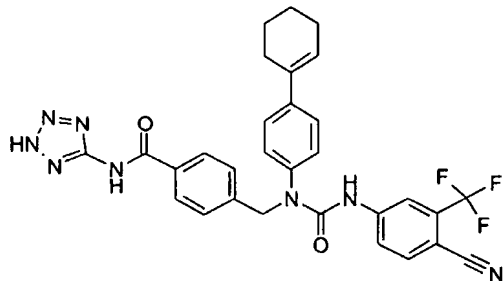
Example 598 (General procedure (Y))4-[1-(4-Cyclohexylphenyl)-3-((1R)-1-phenylethyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

5

^1H NMR (acetone- d_6): δ 1.18-1.48 (m, 9H), 1.68-1.88 (m, 4H), 2.52 (m, 1H), 4.98 (s, 2H), 5.05 (m, 1H), 5.37 (d, 1H), 7.15-7.35 (m, 9H), 7.47 (d, 2H), 8.09 (d, 2H), 11.3 (br, 1H).

LC-MS (APCI, pos.): 524 (M+1).

10

EXAMPLE 599 (general procedure (Y))4-[3-(4-Cyano-3-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

15

HPLC-MS (method B): m/z : 587. R_t = 7.65 min.

^1H NMR (DMSO- d_6): δ 1.55-1.63 (2H, m), 1.68-1.76 (2H, m), 2.17 (2H, broad), 2.35 (2H, broad), 5.05 (2H, s), 6.20 (1H, broad), 7.28 (2H, d), 7.43 (4H, dd), 8.02 (5H, m), 8.18 (1H, s), 9.20 (1H, s), 12.35 (1H, s).

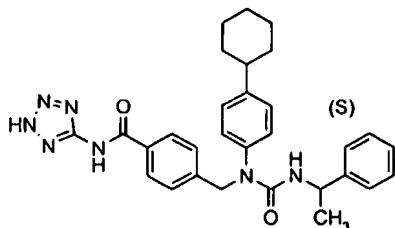
20

Microanalysis: calculated for $\text{C}_{30}\text{H}_{25}\text{F}_3\text{N}_8\text{O}_2 \cdot 0.5 \text{ mol H}_2\text{O}$:

60.50% C; 4.40% H; 18.81% N; Found:

60.80% C; 4.49% H; 18.51% N.

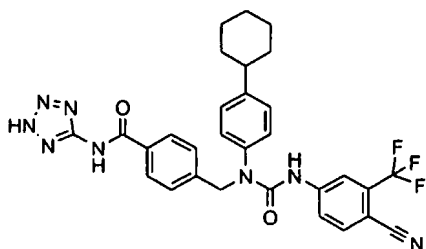
25

Example 596 (General procedure (Y))4-[1-(4-Cyclohexylphenyl)-3-((1S)-1-phenylethyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5 ¹H NMR (DMSO-*d*₆): δ 1.15-1.45 (m, 9H), 1.64-1.80 (m, 5H), 4.82-4.98 (m, 3H), 6.16 (d, 2H), 7.08-7.38 (m, 11H), 7.98 (d, 2H), 11.0 (br, 1H).

LC-MS (APCI, pos.): 524 (M+1).

10 Example 597 (General procedure (Y))

4-[1-(4-Cyclohexylphenyl)-3-(4-cyano-3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 15 ¹H NMR (DMSO-*d*₆): δ 1.10-1.90 (m, 10H), 2.30 (br, 1H), 5.02 (s, 2H), 7.18-7.40 (m, 4H), 7.45 (d, 2H), 7.95-8.20 (m, 5H), 9.14 (s, 1H), 12.34 (s, 1H).

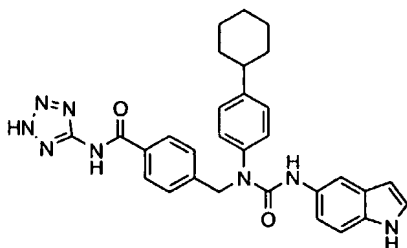
LC-MS (APCI, pos.): 589 (M+1).

^1H NMR ($\text{DMSO}-d_6$): δ 1.52-1.78 (m, 4H), 2.08-2.25 (br, 2H), 2.26-2.40 (br, 2H), 5.00 (s, 2H), 6.19 (br, 1H), 7.14 (s, 1H), 7.22 (d, 2H), 7.36-7.50 (dd, 4H), 7.62 (s, 2H), 8.03 (d, 2H), 12.37 (s, 1H), 16.02 (s, 1H).

5 LC-MS (APCI, pos.): 562 (M+1).

Example 594 (General procedure (Y))

4-[1-(4-Cyclohexylphenyl)-3-(1*H*-indol-5-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



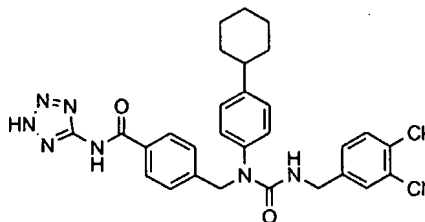
10

^1H NMR ($\text{DMSO}-d_6$): δ 1.12-1.46 (m, 5H), 1.62-1.83 (m, 5H), 5.01 (s, 1H), 6.32 (s, 1H), 7.05-7.08 (q, 1H), 7.17-7.29 (m, 6H), 7.48 (d, 2H), 7.55 (s, 1H), 7.85 (s, 1H), 8.05 (d, 2H), 10.9 (s, 1H), 12.36 (s, 1H), 16.0-16.2 (br, 1H).

15 MS (APCI, pos.): 535 (M+1).

Example 595 (General procedure (Y))

4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorobenzyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



20

^1H NMR: ($\text{DMSO}-d_6$): δ 1.20 (m, 1H), 1.30-1.50 (m, 4H), 1.60-1.70 (m, 5H), 4.21 (s, 2H), 4.89 (s, 2H), 6.60 (m, 1H), 7.14 (d, 2H), 7.21 (d, 3H), 7.39 (d, 2H), 7.46 (s, 1H), 7.56 (d, 1H), 8.03 (d, 2H), 12.30 (s, 1H), 16.00 (brd s, 1H).

25 MS (APCI, pos): 578.1, 579.1, 580.1

¹H NMR (DMSO-*d*₆): δ 1.56 (m, 2H), 1.67 (m, 2H), 2.11 (m, 2H), 2.25 (m, 2H), 3.81 (s, 3H), 4.34 (d, 2H), 5.89 (t, 1H), 6.34 (t, 1H), 6.49 (d, 2H), 7.10 (d, 2H), 7.47 (d, 2H), 7.90 (d, 2H).

5 MS (APCI, pos): 322.1, 323.1.

Step B: The above 4-[(4-cyclohex-1-enylphenylamino)methyl]benzoic acid methyl ester (5 g, 0.015 mol) was dissolved in anhydrous dichloromethane and diisopropylethylamine (5.8 g, 0.045 mol) was added. To this solution was added an isocyanate (eg. 3,5-dichlorophenyl-
10 isocyanate) (0.018 mol). After stirring the reaction mixture for 3 hours, the solution was diluted with ethyl acetate and washed with 1N HCl (2x), water, brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was introduced into a silica gel column and eluted with ethyl acetate/hexane (10/90) to give 4-[3-(3,5-dichlorophenyl-1-(cyclohex-1-enylphenyl)ureidomethyl]benzoic acid methyl ester (4 g).

15

MS (APCI, pos): 509.0, 510.0, 511.1.

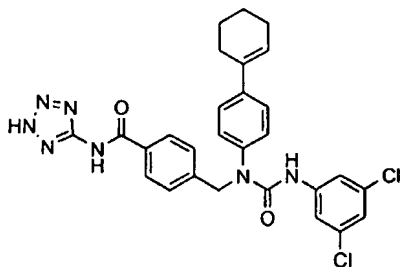
Step C: To a solution of the above 4-[3-(3,5-dichlorophenyl-1-(cyclohex-1-enylphenyl)ureidomethyl]benzoic acid methyl ester (1.5 g, 2 mmol) in THF (30 mL) and methanol (10 mL) was
20 added an excess of 2 M LiOH (10 mL). After stirring the reaction mixture for 3 hours, the solution was concentrated. The residue was taken up in ethyl acetate and washed with 1 N HCl (2x), H₂O (2x), brine, and dried over MgSO₄. Evaporation of the solvent gave the product as an oil. The oil was taken up in dichloromethane. Upon sitting, 4-[3-(3,5-dichlorophenyl-1-(cyclohex-1-enylphenyl)ureidomethyl]benzoic acid (1.2 g, quantitative) crystallized out of so-
25 lution.

Step D: To a solution of the above benzoic acid (0.4 g, 0.81 mmol) in DMF (4 mL) was added HBTU (0.37 g, 0.90 mmol), diisopropylethylamine (0.30 g, 2.4 mmol), and 5-aminotetrazole (0.24 g, 2.4 mmol). After stirring the solution for 16 hours, the reaction mixture was diluted
30 with ethyl acetate and washed with 1N HCl (3x), brine (3x), dried over MgSO₄, filtered, and concentrated to a syrup. By addition of dichloromethane to the oil, the title compound precipitated as a creamy-white solid (200 mg, 0.36 mmol).

R is C₁₋₆-alkyl.

Example 593 (General procedure (Y))

- 5 4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



4-Cyclohex-1-enylaniline:

- 10 A mixture of cyclohexanone (50 g, 0.325 mol), and aniline (95 g, 1 mol) in 12 M HCl (100 mL), and ethanol (15 mL) was refluxed at 110°C for four days. The solution was cooled and diluted with ethyl acetate. The aqueous layer was basified with 6 M NaOH. The organic layer was separate and washed with brine (3x), dried over MgSO₄, and concentrated to give a brown oil. Approximately half of the crude product was introduced into a silica gel column and eluted with 5% ethyl acetate/hexane to obtain the desired product along with aniline. The combined organic fractions were extracted with 1 N HCl and separated. Addition of brine to the aqueous layer precipitated the 4-cyclohex-1-enylaniline as a cream colored solid (9 g).

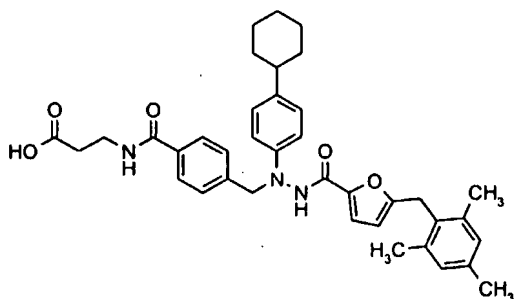
- 20 ¹H NMR (DMSO-*d*₆): δ 1.50-1.60 (m, 2H), 1.60-1.70 (m, 2H), 2.10-2.15 (m, 2H), 2.20-2.30 (brd s, 2H), 5.00 (s, 2H), 5.90 (t, 1H), 6.50 (d, 2H), 7.10 (d, 2H).

- Step A: To a solution of E-NH₂ (eg 4-cyclohexenylaniline, prepared as described above) (0.023 mol) and methyl 4-formylbenzoate (3.77 g, 0.023 mol) in dichloromethane (50 mL) and methanol (15 mL) was added a catalytic amount of acetic acid. After stirring the solution for 3 hours, Na(OAc)₃BH (24 g, 0.115 mol) was added. The reaction was allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate and washed with aqueous sodium bicarbonate (3x), brine (2x), dried over MgSO₄, filtered, and concentrated to give an orange solid. The crude product was introduced into a column of silica gel and eluted with ethyl acetate/hexane (5/95) to give 4-[(4-cyclohex-1-enylphenyl-amino)methyl]benzoic acid methyl ester (5g, 0.015 mol).
- 30

MS (APCI, pos.): 602.3

EXAMPLE 592 (General procedure (X))

3-(4-{N-(4-Cyclohexylphenyl)-N'-[5-(2,4,6-trimethylbenzyl)furan-2-carbonyl]hydrazinomethyl}-
 5 benzoylamino)propionic acid

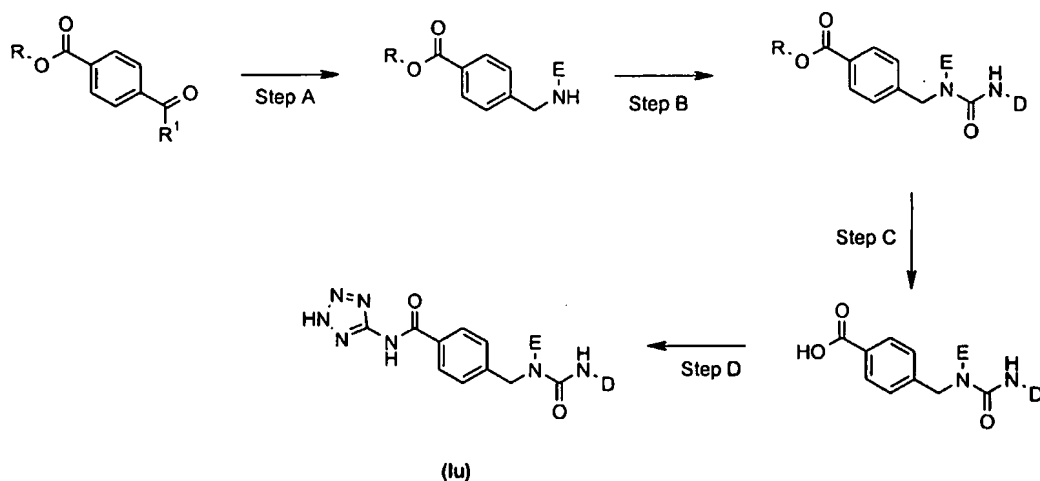


¹H NMR (acetone-*d*₆): δ 1.20-1.38 (m, 5H), 1.70-1.80 (m, 5H), 2.24 (s, 3H), 2.27 (s, 6H), 2.41 (m, 1H), 2.65 (t, 2H), 3.65 (qt, 2H), 3.94 (s, 2H), 4.84 (s, 2H), 5.92 (s, 1H), 6.81 (d, 2H), 6.85 (d, 2H), 7.04 (s, 1H), 7.06 (d, 2H), 7.58 (d, 2H), 7.84 (d, 2H), 9.61 (s, 1H).

MS (APCI, pos): 620.2, 621.3.

General procedure (Y) for solution phase preparation of compounds of general formula (Iu):

15

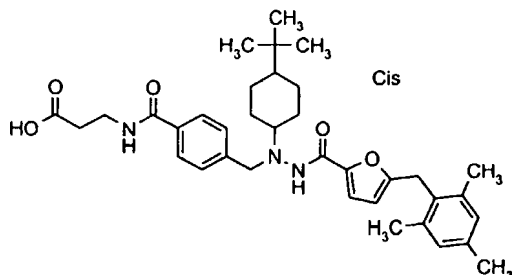


wherein

20 E and D are as defined for formula (I) and

EXAMPLE 591 (General procedure (X))

3-(4-{N-(*cis*-4-*tert*-Butylcyclohexyl)-N'-[5-(2,4,6-trimethylbenzyl)furan-2-carbonyl]hydrazino-methyl}benzoylamino)propionic acid



¹H NMR (DMSO-*d*₆): δ 0.86 (s, 9H), 1.10 (s, 1H), 1.25 – 1.35 (m, 4H), 1.57 (m, 2H), 1.91 (m, 2H), 2.20 (s, 9H), 2.47 (t, 2H), 3.31 (m, 1H), 3.42 (t, 2H), 3.90 (s, 2H), 4.08 (m, 2H), 7.79 (s, 1H), 6.83 (s, 2H), 6.85 (d, 1H), 7.47 (d, 1H), 7.73 (d, 1H), 8.48 (t, 1H), 8.90 (s, 1H), 12.18 (s, 1H).

Preparation of 5-(2,4,6-trimethylbenzyl)furan-2-carbonyl chloride:

Step A: 1,3,5-Trimethylbenzene (6.85 g, 57 mmol), methyl 5-chloromethyl-2-furanoate (2.48 g, 14.2 mmol) and aluminum trichloride (2.46 g, 18 mmol) were refluxed in dichloromethane (30 mL) for 4 h. The reaction was quenched with water, and the two layers were separated.

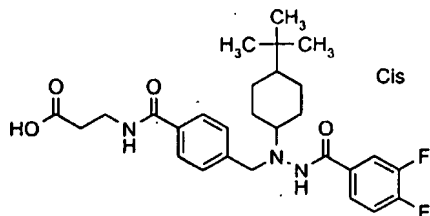
The organic layer was concentrated and passed through a silica gel column. Hexane was used as the mobile phase to elute the product. The 5-(2,4,6-trimethylbenzyl)furan-2-carboxylic acid methyl ester was obtained as a yellow oil (86%).

Step B: The methyl ester (2.9 g, 11.6 mmol) from above was dissolved in methanol (50 mL) and 4 M NaOH (12 mL, 46.5 mmol) was added. The reaction was stirred overnight and made acidic using 1 N HCl. The reaction mixture was concentrated, dissolved in ethyl acetate, washed with brine, and dried over MgSO₄. Upon evaporation of the solvent, the corresponding carboxylic acid was obtained as a light yellow solid (2.7 g, 98%).

Step C: The furanyl carboxylic acid (2.59 g, 0.6 mmol) was dissolved in dichloromethane (20 mL) and thionyl chloride (10 mL, 106 mmol) was added dropwise. The reaction was refluxed for 3 hours and concentrated to dryness. The residue was passed through a silica gel plug-column using dichloromethane. The 5-(2,4,6-trimethylbenzyl)furan-2-carbonyl chloride was obtained as a yellow solid upon evaporation of the solvent (2.7 g, 97%).

EXAMPLE 589 (General procedure (X))

3-{4-[N-(*cis*-4-*tert*-Butylcyclohexyl)-N'-(3,4-difluorobenzoyl)hydrazinomethyl]benzoylamino}-propionic acid



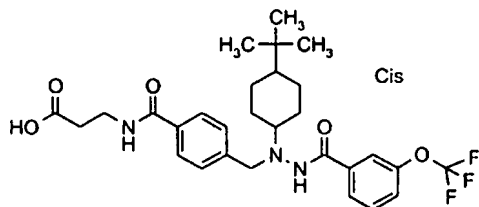
5

^1H NMR (DMSO- d_6): δ 0.85 (s, 9H), 1.03 (m, 1H), 1.36 (m, 4H), 1.59 (m, 2H), 1.92 (m, 2H), 2.44 (t, 2H), 3.41 (t, 2H), 4.04 (m, 3H), 7.46 (m, 4H), 7.60 (q, 1H), 7.72 (d, 2H), 8.47 (t, 1H), 9.30 (s, 1H).

10 MS (APCI, pos.): 516.2.

EXAMPLE 590 (General procedure (X))

3-{4-[N-(*cis*-4-*tert*-Butylcyclohexyl)-N'-(3-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid

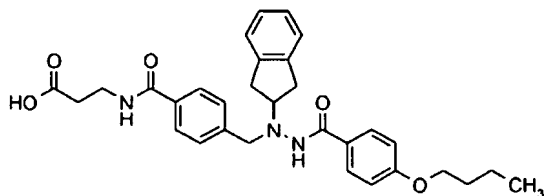


15

^1H NMR (DMSO- d_6): δ 0.87 (s, 9H), 1.08 (m, 1H), 1.38 (m, 4H), 1.61 (m, 2H), 1.95 (m, 2H), 3.41 (t, 2H), 4.10 (m, 2H), 7.45 – 7.53 (m, 3H), 7.62 (d, 1H), 7.74 (d, 1H), 8.44 (t, 1H), 9.38 (s, 1H), 12.19 (s, 1H).

20

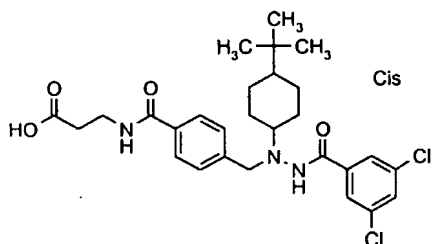
MS (APCI, pos.): 564.2.

EXAMPLE 587 (General procedure (X))**3-{4-[N'-(4-Butoxybenzoyl)-N-indan-2-yl]hydrazinomethyl}benzoylamino}propionic acid**

- 5 ¹H NMR (DMSO-*d*₆): δ 0.91 (t, 3H), 1.41 (quintet, 2H), 1.67 (quintet, 2H), 2.49 (t, 2H), 3.96 (t, 2H), 4.15 (m, 2H), 6.88 (d, 2H), 7.09 - 7.18 (m, 2H), 7.10 - 7.20 (m, 2H), 7.50 (t, 4H), 7.72 (d, 2H), 8.47 (t, 1H), 9.13 (s, 1H).

MS (APCI, pos.): 530.2.

10

EXAMPLE 588 (General procedure (X))**3-{4-[N-(*cis*-4-*tert*-Butylcyclohexyl)-N'-(3,5-dichlorobenzoyl)]hydrazinomethyl}benzoylamino}-propionic acid**

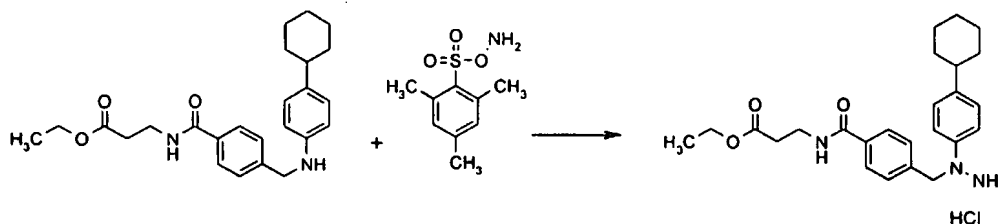
15

- ¹H NMR (DMSO-*d*₆): δ 0.85 (s, 9H), 1.04 (m, 1H), 1.37 (m, 4H), 1.58 (m, 2H), 1.92 (m, 2H), 2.44 (t, 2H), 3.42 (t, 2H), 4.16 (m, 3H), 7.44 (d, 2H), 7.58 (s, 2H), 7.74 (d, 2H), 7.75 (s, 1H), 8.48 (t, 1H), 9.42 (s, 1H).

- 20 MS (APCI, pos.): 548.2, 550.1.

APCI $[M - NH_2]^+ = 199.0$.

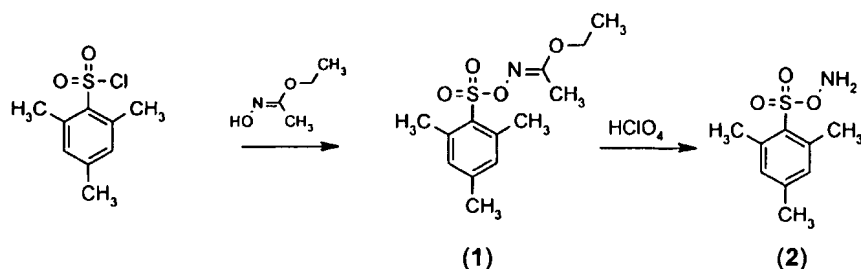
Preparation of 3-{4-[N-(4-cyclohexylphenyl)hydrazinomethyl]benzoylamino}propionic acid
 5 ethyl ester hydrochloride:



3-{4-[(4-Cyclohexylphenylamino)methyl]benzoylamino}propionic acid ethyl ester (0.6 g, 1.47
 10 mmol) was dissolved in dichloromethane (12 mL) and O-mesitylenesulfonylhydroxylamine
 (0.79 g, 3.68 mmol) was added while stirring at 0°C. The solution stirred for 20 min. The solu-
 tion was concentrated to 1/4 its original volume and loaded onto a silica gel column packed
 with 25% ethyl acetate/hexane. The product was eluted with 5% methanol/ethyl acetate. To
 each 50 mL fraction, which contained product, 4 mL of 1 M HCl/diethyl ether was added. The
 15 fractions were combined and concentrated to give a rust colored solid. The solid was dis-
 solved in ethyl acetate (10 mL) and hexane (20 mL) was added. A white precipitate formed
 and was collected by filtration followed by rinsing with ethyl acetate to give 3-{4-[N-(4-cyclo-
 hexylphenyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride as a
 white solid (0.1 g, 15% yield). The product was stored in a freezer at -70°C until the next
 20 step.

APCI $[M]^+ = 424.2$.

Examples of products prepared according to general procedure (X).



Preparation of (1): See Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

5 Mesitylenesulfonyl chloride (6.75 g, 31 mmol) was added to a solution of ethyl acetohydroxamate (3.2 g, 31 mmol) and triethylamine (4.6 mL) in DMF (25 mL) dropwise over a period of 20 minutes while stirring on an ice bath. Stirring was continued for an additional 20 min at 0 – 10°C and the reaction mixture was poured into ice/water (100 mL). The solution was stirred for 10 min and a white solid precipitated. The product was collected by vacuum filtration and
10 washed with water (200 mL). The solid was dissolved in diethyl ether (200 mL) and dried over MgSO₄. The solution was concentrated to give an off white solid which was dissolved in hot hexane. White crystals formed by placing the solution in a -30°C freezer overnight. The crystals were collected by filtration and dried with suction for one hour affording the product, (1) (6g, 90% yield).

15

¹H NMR (300 MHz, DMSO-*d*₆): δ 7.71 (s, 2H), 3.84 (q, 2H), 2.56 (s, 6H), 2.29 (s, 3H), 2.01 (s, 3H), 1.12 (t, 3H).

APCI $[M]^+ = 286.1$.

20

Preparation of (2): See Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

To a solution of (1) (2 g, 6.7 mmol) in dioxane (8 mL) was added 70% perchloric acid (1.2 mL) dropwise while stirring at 0°C over a period of 10 minutes. The solution stirred for an additional 10 minutes at 0 – 10°C and the reaction mixture was poured into ice/water (100 mL). The solution was stirred for 10 min and a white solid precipitated. The solid was collected by filtration, washed with cold water (200 mL) followed by cold hexane (100 mL) and dried by maintaining suction for 1 hour to give the product, (2), as a white powder (1.4 g, 97% yield).

30 ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.24 (bs, 2H), 6.78 (s, 2H), 2.51 (s, 6H), 2.18 (s, 3H).

forded *N'*-(1-ethylpentyl)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester as a white foam (7 g, 87% yield): APCI [M]⁺ = 367.2.

The above ethylpentyl compound (7 g, 19.1 mmol) was dissolved in acetonitrile (200 mL) and the 3-(4-chloromethylbenzoylamino)propionic acid ethyl ester (5.7 g, 21 mmol) was added. Potassium carbonate (7.9 g, 57.3 mmol) and sodium iodide (catalytic) were added and the solution was stirred at 50°C for 36 hours. The solution was diluted with ethyl acetate (800 mL) and washed with aqueous sat NaHCO₃ (3 x 300 mL), brine (3 x 300 mL), dried over MgSO₄ and concentrated to give a beige foam. Purification by silica gel flash chromatography eluting with 60% ethyl acetate/hexane to give 3-{4-[*N'*-(1-ethylpentyl)-*N'*-(9*H*-fluoren-9-ylmethylmethoxycarbonyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester as a white foam (6 g, 52.4% yield).

¹H NMR (300 MHz, DMSO-*d*₆): δ 9.51 (t, 1H), 9.39 (s, 1H), 7.87 (d, 2H), 7.71 (d, 2H), 7.58 (d, 2H), 7.39 (m, 4H), 7.28 (m, 2H), 4.28 (m, 2H), 4.19 (d, 2H), 4.05 (q, 2H), 3.89 (s, 2H), 3.48 (q, 2H), 2.56 (m, 3H), 1.19 (m, 12H), 0.80 (m, 6H).

APCI [M]⁺ = 600.3.

The above propionic acid ethyl ester compound (2.5 g, 4.2 mmol) was dissolved in DMF (15 mL) and piperidine (1.5 mL) was added while stirring at room temperature. TLC showed complete deprotection after 10 minutes. The solution was diluted with ethyl acetate (350 mL) and washed with H₂O (2 x 100 mL), brine (1 x 100 mL) and the organic layer was loaded directly onto a silica gel column packed with 20% ethyl acetate/hexane. 1 L of 20% ethyl acetate/hexane was flushed through the column followed by 50% ethyl acetate/hexane, followed by 80% ethyl acetate/hexane, which eluded the product. To each 50 mL fraction, which contained product, 4 mL of 1 M HCl/diethyl ether was added. The fractions were combined and concentrated to give 3-{4-[*N'*-(1-ethylpentyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride as an orange solid (1.2 g, 69.6% yield). The compound was used immediately in the next step.

APCI [M]⁺ = 378.2.

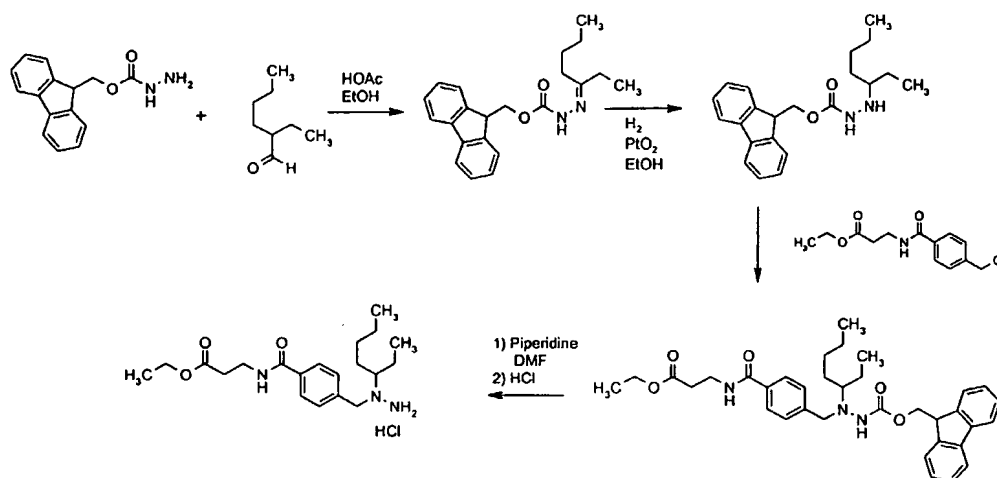
product, 4 mL of 1 M HCl/diethyl ether was added. The fractions were combined and concentrated to give 3-{4-[*N*-4-*cis*-*tert*-butylcyclohexyl]hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride as an orange solid (3.6 g, 85.5% yield). The compound was used immediately in the next step.

5

APCI $[M]^+ = 404.3$.

Preparation of 3-{4-[*N*-(1-ethylpentyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride:

10



Fmoc-hydrazide (12 g, 47.2 mmol) was dissolved in ethanol (400 mL) and 2-ethylhexanal (7.3 g, 56.6 mmol) was added. Glacial acetic acid (4 mL) was added and the solution stirred for 18 h at room temperature. *N'*-(1-ethylpentylidene)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester precipitated out of solution, and was collected by vacuum filtration and rinsed with ethanol to give beige needles (8 g, 47% yield).

20

APCI $[M]^+ = 365.2$.

25

The above ethylpentylidene compound (8 g, 21.9 mmol) was dissolved in anhydrous ethanol (600 mL) and PtO₂ (150 mg, 0.68 mmol) was added. The solution was stirred under a H₂ atmosphere (1 atm) at room temperature for 6 hours. The solution was passed through a bed of silica gel followed by two volumes of ethyl acetate and concentrated to give a white foam. Purification by silica gel flash chromatography eluting with 15% ethyl acetate/hexane af-

foam. Purification by silica gel flash chromatography eluting with 10% ethyl acetate/hexane afforded *N'*-(4-*cis*-*tert*-butylcyclohexyl)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester as a white foam (12 g, 71% yield). By eluting with 15% ethyl acetate/hexane the corresponding *trans* isomer, *N'*-(4-*trans*-*tert*-butylcyclohexyl)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester, is obtained (2 g, 12% yield) as a white foam.

cis isomer: ¹H NMR (300 MHz) (CDCl₃): δ 7.78 (d, 2H), 7.59 (d, 2H), 7.43 (m, 2H), 7.34 (m, 2H), 4.48 (d, 2H), 4.25 (t, 1H), 3.21 (m, 1H), 1.80 (m, 2H), 1.36 (m, 6H), 1.01 (m, 1H), 0.87 (s, 9H).

APCI [M]⁺ = 393.2.

The above *cis* isomer (8 g, 20 mmol) was dissolved in acetonitrile (200 mL) and the 3-(4-chloromethylbenzoylamino)propionic acid ethyl ester (6 g, 22.4 mmol), potassium carbonate (8.4 g, 61 mmol), and sodium iodide (catalytic) were added and the solution was stirred at 50°C for 36 hours. The solution was diluted with ethyl acetate (800 mL) and washed with aqueous sat NaHCO₃ (3 x 300 mL), brine (3 x 300 mL), dried over MgSO₄ and concentrated to give a golden foam. Purification by silica gel flash chromatography eluting with 50% ethyl acetate/hexane afforded 3-{4-[*N*-(4-*cis*-*tert*-butylcyclohexyl)-*N'*-(9*H*-fluoren-9-ylmethyl-methoxycarbonyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester as a white foam (6 g, 47% yield).

¹H NMR (300 MHz, DMSO-*d*₆): δ 8.52 (t, 1H), 8.36 (s, 1H), 7.84 (d, 2H), 7.53 (d, 2H), 7.51 (t, 2H), 7.42 (m, 4H), 7.25 (t, 2H), 4.17 (d, 2H), 4.04 (m, 4H), 3.48 (m, 2H), 3.13 (m, 1H), 2.57 (d, 2H), 1.92 (m, 2H), 1.78 (m, 2H), 1.33 (m, 4H), 1.01 (m, 1H), 0.85 (s, 9H).

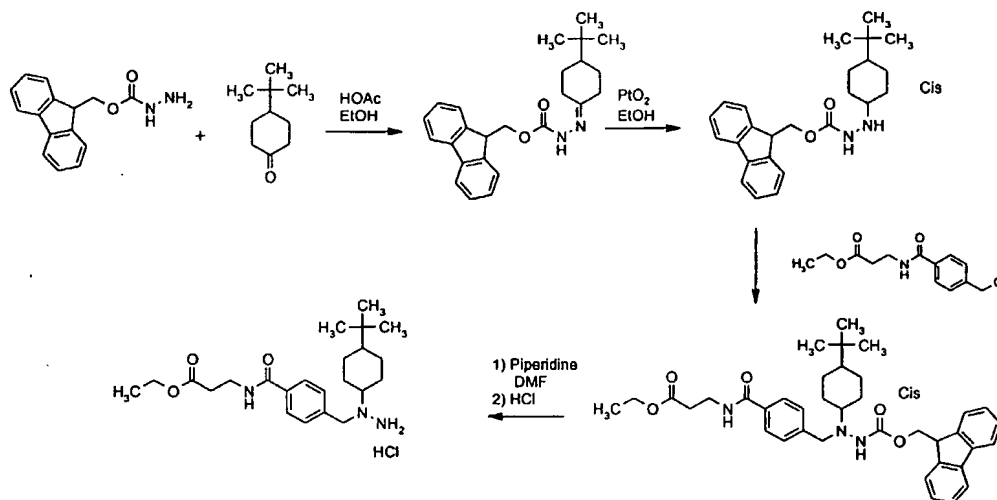
APCI [M]⁺ = 626.3.

The above propionic acid ethyl ester (6 g, 9.6 mmol) was dissolved in DMF (15 mL) and piperidine (1.5 mL) was added while stirring at room temperature. TLC showed complete conversion after 10 minutes. The solution was diluted with ethyl acetate (350 mL) and washed with water (2 x 100 mL), brine (1 x 100 mL) and the organic layer was loaded directly onto a silica gel column packed with 20% ethyl acetate/hexane. 1 L of 20% ethyl acetate/hexane was flushed through the column followed by 50% ethyl acetate/hexane, followed by 80% ethyl acetate/hexane which eluded the product. To each 50 mL fraction that contained

The starting materials (hydrazines) can be prepared as follows:

Preparation of 3-{4-[*N*-4-*cis*-*tert*-butylcyclohexyl]hydrazinomethyl}benzoylamino}propionic acid ethyl ester hydrochloride:

5



Fmoc-hydrazide (12 g, 47.2 mmol) was dissolved in ethanol (400 mL) and 4-*tert*-butylcyclohexanone (8.73 g, 56.6 mmol) was added. Glacial acetic acid (4 mL) was added and the solution stirred for 18 hours at room temperature. The solution was concentrated to 1/4 its original volume and diluted with ethyl acetate (600 mL). The organic layer was washed with sat. aq NaHCO₃ (1 x 200 mL), brine (2 x 200 mL), dried over MgSO₄ and concentrated to give a yellow foam. Purification by silica gel flash chromatography eluting with 20% ethyl acetate/hexane to give *N'*-(4-*tert*-butylcyclohexylidene)hydrazinecarboxylic acid 9*H*-fluoren-9-ylethyl ester as a beige foam (16.9 g, 92% yield).

¹H NMR (300 MHz, DMSO-*d*₆): δ 9.98 (s, 1H), 7.89 (d, 2H), 7.48 (d, 2H), 7.43 (m, 2H), 7.31 (m, 2H), 4.29 (d, 2H), 2.12 (m, 1H), 1.80 (m, 4H), 1.12 (m, 4H), 0.86 (m, 10H).

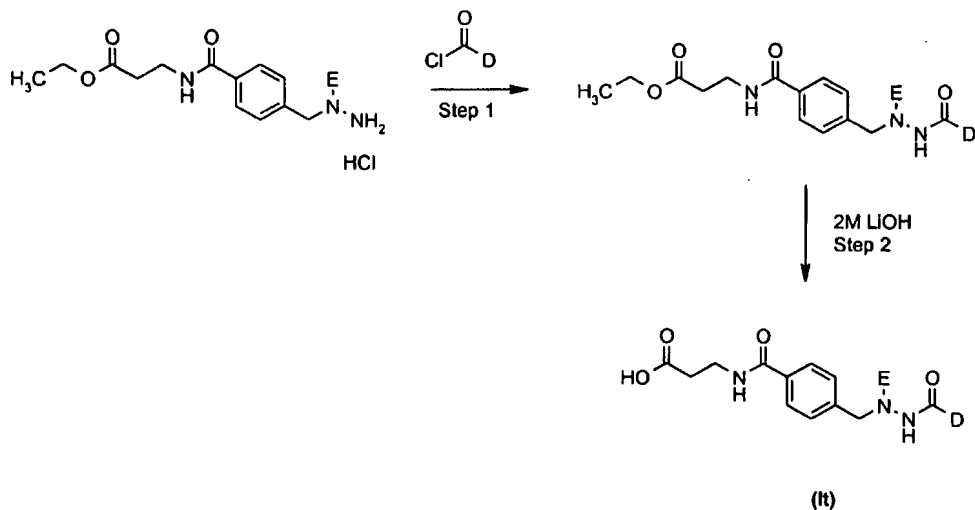
APCI [M]⁺ = 391.2.

The above cyclohexylidene compound (16.9 g, 43.3 mmol) was dissolved in anhydrous ethanol (400 mL) and PtO₂ (200 mg, 0.9 mmol) was added. The solution was stirred under a H₂ atmosphere (1 atm) at room temperature for 18 hours. The solution was passed through a bed of silica gel followed by two volumes of ethyl acetate and concentrated to give a yellow

MS (APCI, pos): 549.2, 550.2

General procedure (X) for solution phase synthesis of compounds of the general formula (It):

5



wherein D and E are as defined for formula (I).

- 10 Step 1: Solutions of the desired acid chloride (0.01 mmol) in dichloroethane are placed into the appropriate wells of a 1 mL deep-well plate. A solution of the hydrazide (0.01 mmol) in dichloroethane, and a solution of triethylamine (0.05 mmol) in dichloroethane are then added into all of the wells of the deep-well plate. The reaction mixtures are allowed to react for 12 hours.

15

Step 2: To the wells above are added excess aqueous 2M LiOH. After stirring the plates for at least three hours, the solvents are removed to afford the crude products.

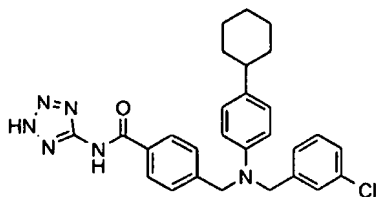
445

¹H NMR: (DMSO-*d*₆): δ 1.16-1.27 (m, 5H), 1.69-1.72 (m, 5H), 2.29 (brd m, 1H), 4.71 (s, 2H), 4.77 (s, 2H), 6.54 (d, 2H), 6.94 (d, 2H), 7.28 (s, 2H), 7.42 (m, 4H), 8.03 (d, 2H), 12.25 (brd s, 1H), 16.00 (brd s, 1H).

5 MS (APCI, pos): 545.2

EXAMPLE 585 (General procedure (W))

4-(((3-Chlorobenzyl)-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



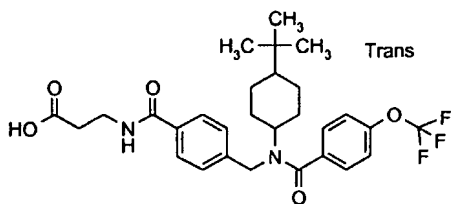
10

¹H NMR: (DMSO-*d*₆): δ 1.16-1.24 (m, 5H), 1.60-1.70 (m, 5H), 2.30 (m, 1H), 4.71 (s, 2H), 4.77 (d, 2H), 6.54 (d, 2H), 6.93 (d, 2H), 7.21 (d, 1H), 7.29 (m, 2H), 7.34 (d, 1H), 7.41 (d, 2H), 8.05 (d, 2H), 12.36 (s, 1H), 16.04 (brd s, 1H).

15 MS (APCI, pos): 501.2, 503.1

EXAMPLE 586

3-(4-(((trans-4-tert-Butylcyclohexyl)-(4-trifluoromethoxybenzoyl)amino)methyl)benzoylamino)propionic acid

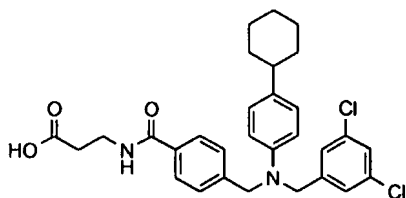


20

This compound was made from 3-{4-[(*trans*-4-*tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester with trifluoromethoxybenzoyl chloride according to a typical acylation procedure, followed by hydrolysis.

25

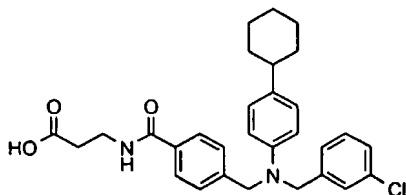
¹H NMR: (CDCl₃): δ 0.76 (m, 10H), 1.46 (d, 2H), 1.60-1.80 (brd m, 6H), 2.60 (t, 2H), 3.56 (m, 1H), 3.63 (qt, 2H), 4.69 (s, 2H), 7.18 (m, 2H), 7.32 (m, 2H), 7.45 (m, 2H), 7.70 (d, 2H).

EXAMPLE 582 (General procedure (W))**3-(4-(((4-Cyclohexylphenyl)-(3,5-dichlorobenzyl)amino)methyl)benzoylamino)propionic acid**

- 5 ¹H NMR: (DMSO-*d*₆): δ 1.20-1.28 (m, 5H), 1.67-1.71 (m, 5H), 2.30 (m, 1H), 2.46 (t, 2H), 3.44 (qt, 2H), 4.69 (s, 2H), 4.73 (s, 2H), 6.53 (d, 2H), 6.94 (d, 2H), 7.28 (s, 2H), 7.31 (d, 2H), 7.47 (s, 1H), 7.77 (d, 2H), 8.49 (brd t, 1H).

MS (APCI, pos): 539.2, 541.0, 542.0

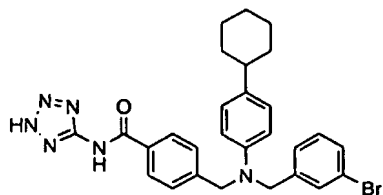
10

EXAMPLE 583 (General procedure (W))**3-(4-(((3-Chlorobenzyl)-(4-cyclohexylphenyl)amino)methyl)benzoylamino)propionic acid**

- 15 ¹H NMR: (DMSO-*d*₆): δ 1.05-1.38 (m, 5H), 1.57-1.80(m, 5H), 2.29 (br, 1H), 2.46 (t, 2H), 3.42 (q, 2H), 4.68 (d, 4H), 6.53(d, 2H), 6.92 (d, 2H), 7.18-7.45 (m, 5H), 7.76(d, 2H), 8.46 (t, 1H), 12.3 (br, 1H).

LC-MS (APCI, pos.): 505 (M+1).

20

EXAMPLE 584 (General procedure (W))**4-(((3-Bromobenzyl)-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)benzamide**

when the reaction was complete. The product from step 4 was used in the next step without further purification or characterisation.

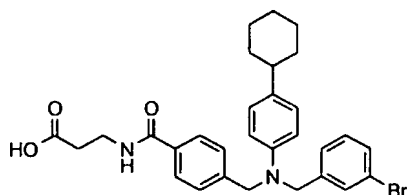
Step 5: To a solution of the product from step 4 (1.7 g) in methanol (30 mL) was added 2M aqueous lithium hydroxide (10 mL). The mixture was stirred at room temperature for 30 minutes and then diluted with water and washed with diethyl ether (2 × 30 mL). The aqueous layer was acidified with dilute hydrochloric acid and extracted with diethyl ether. The organic extract was dried (MgSO₄) and concentrated to give a crude product, which was purified by HPLC to afford the title compound.

¹H NMR: (DMSO-*d*₆): δ 0.78 (s, 9H), 0.89 (m, 3H), 1.29 (qt, 2H), 1.77 (d, 2H), 1.85 (d, 2H), 2.31 (t, 1H), 2.47 (t, 2H), 3.42 (qt, 2H), 3.60 (s, 2H), 3.62 (s, 2H), 7.36 (m, 3H), 7.40 (d, 2H), 7.76 (d, 2H), 8.47 (t, 1H).

MS (APCI, pos): 519.2, 521.1

EXAMPLE 581 (General procedure (W))

3-(4-[[[(3-Bromobenzyl)-(4-cyclohexylphenyl)amino]methyl]benzoylamino]propionic acid



¹H NMR: (MeOH-*d*₄): δ 1.34–1.37 (m, 5H), 1.70–1.77 (m, 5H), 2.20 (m, 1H), 2.56 (t, 2H), 3.60 (t, 2H), 4.11 (s, 2H), 4.65 (s, 2H), 6.61 (d, 2H), 6.95 (d, 2H), 7.20 (d, 2H), 7.30 (m, 4H), 7.72 (d, 2H).

MS (APCI, pos): 551.1, 552.0

Step 2: To a solution of the product obtained from step 1 (1.15 g, 3.8 mmol) and 3,5-dichlorobenzylchloride (0.74 g, 3.8 mmol) in acetonitrile (50 mL) was added potassium carbonate (0.79 g 5.7 mmol). The mixture was refluxed overnight. After cooling to room temperature, water (100 mL) was added, and the mixture was extracted with diethyl ether. The organic extract was dried (MgSO₄) and concentrated to give a crude product, which was purified by column chromatography to afford 1.7 g (97%) of 4-[[[(4-*tert*-butylcyclohexyl)-(3,5-dichlorobenzyl)amino]methyl]benzoic acid methyl ester.

¹H NMR (CDCl₃): δ 0.85(s, 9H), 1.22-1.59(m, 5H), 1.78-1.98(m, 4H), 2.41(m, 1H), 3.57(s, 2H), 3.66(s, 2H), 3.87(s, 3H), 7.18(s, 1H), 7.24(s, 2H), 7.40(d, 2H), 9.08(d, 2H).

LC-MS (APCI, pos.): 463(M+1).

Alternatively, step 2 can be performed as a reductive alkylation using an aldehyde (D-CHO instead of D-CH₂-Lea) together with a reducing agent such as sodium cyanoborohydride.

Step 3: To a solution of the product from step 2 (1.7 g) in methanol (30 mL) was added 10% aqueous potassium hydroxide (10 mL) and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with diethyl ether (2 × 30 mL). The aqueous layer was neutralised with dilute hydrochloric acid, and extracted with diethyl ether. The organic extract was dried (MgSO₄) and concentrated to give 1.6 g (100%) of 4-[[[(4-*tert*-butylcyclohexyl)-(3,5-dichlorobenzyl)amino]methyl]benzoic acid .

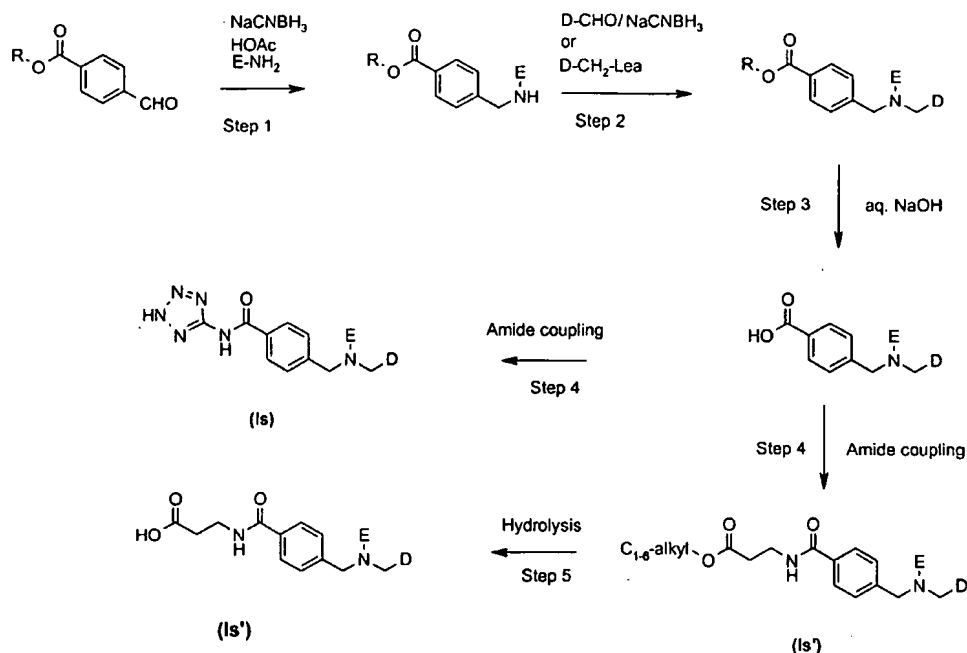
¹H NMR (CDCl₃, δ): 8.01(s, 9H), 0.9-1.10(m, 4H), 1.66(m, 1H), 1.89(m, 2H), 2.32(m, 2H), 3.10(m, 1H), 4.21(s, 2H), 4.52(m, 2H), 7.58(s, 1H), 7.60-7.70(m, 3H), 7.88(d, 2H), 11.0(br, 1H).

LC-MS (APCI, pos.): 449 (M+1).

30

Step 4: To a solution of the product obtained in step 3 (1.6 g, 3.7 mmol) in DMF (30 mL) was added HBTU (1.5 g, 4.0 mmol) and diisopropylethylamine (1 g, 8 mmol). The mixture was stirred at 0°C for 30 minutes, and then β-alanine ethyl ester hydrochloride (1.2 g, 8 mmol) was added at 0°C. The reaction was monitored by TLC, and DMF was evaporated in vacuo

General procedure (W) for the solution phase synthesis of compounds of general formulae (Is) and (Is'):



5

wherein R is C_{1-6} -alkyl,

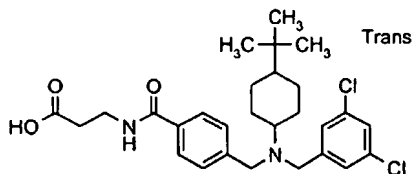
D and E are as defined in general formula (I) and

10 Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

The general procedure (W) is illustrated by the following example.

EXAMPLE 580 (general procedure (W))

15 3-(4-(((trans-4-tert-Butylcyclohexyl)-(3,5-dichlorobenzyl)amino)methyl)benzoylamino)-propionic acid



Step 1: This step is identical to that described in general procedure (K), step 1.

To a suspension of above 4-[(2*H*-tetrazol-5-ylamino)methyl]benzaldehyde hydrochloride (1.0 g, 4.17 mmol) in methanol (10 mL) was added triethylamine, until a clear solution was obtained. 4-(*tert*-butylcyclohexyl)amine (*cis/trans*-mixture) (650 mg, 4.17 mmol) was added. 5 Acetic acid was added to adjust the pH to 6. The mixture was stirred at room temperature for 16 hours, and NaBH(OAc)₃ (1.0 g, 4.7 mmol) was added. After stirring for 16 hours at room temperature, the mixture was filtered and concentrated. The crude {4-[(4-*tert*-butylcyclohexylamino)methyl]benzyl}-(2*H*-tetrazol-5-yl)amine was used without further purification in the next step.

10

MS (APCI, pos.): 343.2 (M+1).

To a solution of above amine (288 mg, 0.84 mmol) in dichloromethane (10 mL) was added 4-trifluoromethoxyphenylisocyanate (180 mg, 0.84 mmol). After stirring for 16 hours at room 15 temperature, the title compound (75 mg) crystallized out as a mixture of *cis* and *trans*-isomers.

¹H NMR (DMSO-*d*₆): δ 0.80, 0.82 (2 s, 9H), 0.92 (m, 1H), 1.09 (q, 2H), 1.34 - 1.51 (m, 3H), 1.64 - 1.75 (m, 3H), 4.00 (m, 0.75H), 4.21 (m, 0.25H), 4.35 (d, 2H), 4.53 (s, 1.5H), 4.64 (s, 20 0.5H), 7.14 (d, 1H), 7.16 - 7.29 (m, 6H), 7.53 (d, 2H), 7.55 (s, 1H), 8.46 (s, 0.75H), 8.55 (s, 0.25H).

MS (APCI, pos.): 546.2 (M+1).

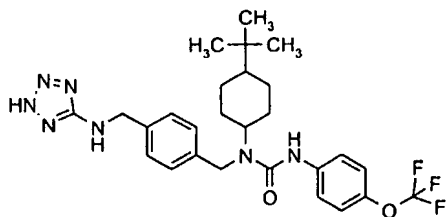
To a solution of above carboxylic acid (400 mg, 0.90 mmol) in DMF (7 mL) was added diisopropylethylamine (0.28 mL, 206 mg, 1.60 mmol) and HBTU (360 mg, 0.96 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (136 mg, 1.60 mmol) was added. After stirring for 72 hours, the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography (hexanes, ethyl acetate, 1:2) afforded 120 mg of the title compound.

¹H NMR (DMSO-*d*₆): δ 0.83 (s, 9H), 0.96 (q, 1H), 1.12 (q, 2H), 1.50 (q, 2H), 1.73 (m, 4H), 3.96 (m, 1H), 4.70 (s, 2H), 7.14 (d, 1H), 7.24 (d, 2H), 7.55 (d, 2H), 8.04 (d, 1H), 8.64 (s, 1 H), 12.37 (s, 1 H), 15.92 (s, 1H).

MS (APCI, pos.): 566.1 (M+1).

15 EXAMPLE 579

1-(4-*tert*-Butylcyclohexyl)-1-[4-[(2*H*-tetrazol-5-ylamino)methyl]benzyl]-3-(4-trifluoromethoxyphenyl)urea



20 To a suspension of 5-aminotetrazole (4.25g, 50 mmol) in ethanol (25 mL) was added triethylamine (6.9 mL, 5.05 g, 50 mmol). To the clear solution was added terephthaldehyde mono (diethyl acetal) (10.4 g, 50 mmol). After stirring for 2 hours at room temperature, platinum oxide (150 mg) was added, and the mixture was hydrogenated at 50 psi for 16 hours. The catalyst was filtered off, and the filtrate was concentrated. On addition of water and conc. HCl, 25 the residue crystallized. The solid was filtered off to give 4-[(2*H*-tetrazol-5-ylamino)methyl]benzaldehyde hydrochloride.

¹H NMR (DMSO-*d*₆): δ 4.50 (d, 2 H), 7.33 (s, 1H), 7.54 (d, 2 H), 7.66 (t, 1H) 7.88 (d, 2H), 9.98 (s, 1H).

30

MS (APCI, pos.): 204.0 (M+1).

The *trans*-imine from above (1.82 g, 5.9 mmol) was dissolved in dichloromethane (20 mL), and NaBH(OAc)₃ (1.5 g, 7.1 mmol) was added. The mixture was stirred for 16 hours at room temperature, diluted with water (20 mL), washed with NaHCO₃ solution (20 mL), brine (20 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (hexanes, ethyl acetate, 2:1) provided 692 mg of 5-[(4-*trans-tert*-butylcyclohexylamino)methyl]thiophene-2-carboxylic acid methyl ester.

¹H NMR (CDCl₃): δ 0.85 (s, 9H), 1.00 - 1.15 (m, 5H), 1.80 (m, 2H), 2.00 (m, 2H), 2.44 (m, 1H), 3.88 (s, 3H), 4.04 (s, 2H), 6.92 (d, 1H), 7.68 (d, 1H).

MS (APCI, pos.): 310.1 (M+1).

The above amine (692 mg, 2.23 mmol) was dissolved in dichloromethane (12 mL), and 4-trifluoromethoxyphenylisocyanate (454 mg, 2.23 mmol) was added. After stirring for 16 hours at room temperature, the mixture was concentrated. Flash chromatography (hexanes, ethyl acetate, 5:1) provided 1.1 g of 5-[1-(4-*trans-tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carboxylic acid methyl ester.

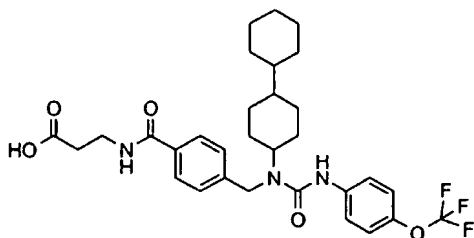
¹H NMR (CDCl₃): δ 0.87 (s, 9H), 0.98 (t, 1H), 1.12 - 1.27 (m, 2H), 1.48 (q, 2H), 1.88 (m, 4H), 3.89 (s, 3H), 4.04 (s, 2H), 3.98 (m, 1H), 4.65 (s, 2H), 6.42 (s, 1H), 7.06 (d, 1H), 7.13 (d, 2H), 7.37 (d, 2H), 7.71 (d, 1H). MS (APCI, pos.): 513.1 (M+1).

The above ester (1.1 g, 2.14 mmol) was dissolved in THF (15 mL) and methanol (2 mL) and 2M LiOH (5 mL) was added. The mixture was stirred at room temperature for 16 hours, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (MgSO₄), and concentrated. The residue crystallized from hexane, ethyl acetate to afford 745 mg of 5-[1-(4-*trans-tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carboxylic acid as a white solid.

¹H NMR (DMSO-*d*₆): δ 0.85 (s, 9H), 0.90 (q, 1H), 1.09 (q, 2H), 1.53 (q, 2H), 1.68 (m, 4H), 4.02 (m, 1H), 4.68 (s, 2H), 7.07 (d, 1H), 7.25 (d, 2H), 7.54 (d, 1H), 7.56 (d, 2H), 8.63 (s, 1H).

EXAMPLE 577

3-{4-[1-(4-Cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



5

This compound was prepared similarly as described in examples 575 and 576 using the ethyl ester of 3-aminopropionate instead of 5-aminotetrazole followed by hydrolysis.

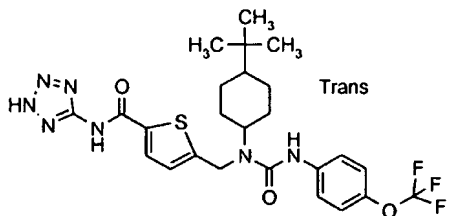
¹H NMR (DMSO-*d*₆): δ 0.07-0.08 (m, 2H), 1.05-1.13 (m, 5H), 1.32-1.50 (m, 6H), 1.64-1.91 (m, 7H), 2.51 (t, 2H), 3.48 (qt, 2H), 4.07 (brd m, 1H), 4.62 (s, 2H), 7.21 (d, 2H), 7.33 (d, 2H), 7.52 (d, 2H), 7.76 (d, 2H), 8.46 (brd t, 1H), 8.53 (brd s, 1H), 12.16 (brd s, 1H).

10

MS (APCI, pos): 590.3, 544.0, 518.2, 387.2, 388.2.

15 **EXAMPLE 578**

5-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carboxylic acid (2*H*-tetrazol-5-yl)amide



20 To a solution of methyl 5-formyl-thiophene-2-carboxylate (1.65 g, 9.6 mmol) (prepared according to C. Goddard, J. Heterocycl. Chem. 28, 1991, 17-28) in methanol (10 mL) was added 4-(*tert*-butylcyclohexyl)amine (*cis/trans* mixture). After standing at room temperature for 16 hours the precipitate was filtered off by suction to afford 1.82 g of 5-[(4-*trans*-*tert*-butylcyclohexylimino)methyl]thiophene-2-carboxylic acid methyl ester.

25

¹H NMR (CDCl₃): δ 0.87 (s, 9H), 1.07 - 1.17 (m, 3H), 1.51 - 1.63 (m, 2H), 1.77 - 1.88 (m, 4H), 3.13 (m, 1H), 3.88 (s, 3H), 7.25 (d, 1H), 7.72 (d, 1H), 8.36 (s, 1H).

MS (APCI, pos.): 533.2 (M+1).

5 The above ester (487 mg, 0.99 mmol) was dissolved in THF (10 mL) and methanol (5 mL) and 1M KOH (4 mL) was added. The mixture was stirred at 80°C for 90 minutes, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (MgSO₄), and concentrated. The residue crystallized from hexane, ethyl acetate to afford 380 mg of 4-[1-(*trans*-4-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid white solid.

10

¹H NMR (DMSO-*d*₆): δ 0.91 - 1.15 (m, 10H), 1.37 (q, 2H), 1.63 (m, 8H), 4.04 (m, 1H), 4.60 (s, 2H), 7.21 (d, 2H), 7.34 (d, 2H), 7.53 (d, 2H), 7.86 (d, 2H), 8.54 (s, 1 H).

MS (APCI, pos.): 519.1 (M+1).

15

To a solution of above benzoic acid (380 mg, 0.71 mmol) in DMF (10 mL) was added diisopropylethylamine (0.38 mL, 275 mg, 2.12 mmol) and HBTU (320 mg, 0.86 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (150 mg, 1.45 mmol) was added. The mixture was stirred for 16 hours, and the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄), and concentrated. The residue was dissolved in dichloromethane. On addition of ether, the title compound crystallized. Yield: 215 mg.

20

¹H NMR (DMSO-*d*₆): δ 0.82 - 1.18 (m, 10H), 1.40 (q, 2H), 1.63 (m, 8H), 4.03 (m, 1H), 4.63 (s, 2H), 7.21 (d, 2H), 7.41 (d, 2H), 7.57 (d, 2H), 8.03 (d, 2H), 8.56 (s, 1 H), 12.32 (s, 1H), 15.95 (s, 1H).

25

MS (APCI, pos.): 586.1 (M+1).

¹H NMR (DMSO-*d*₆): δ 0.66 - 1.80 (m, 20H), 4.04 (m, 1H), 4.62 (s, 2H), 7.20 (d, 2H), 7.37 (d, 2H), 7.51 (d, 2H), 7.86 (d, 2H), 8.54 (s, 1H). MS (APCI, pos.): 519.1 (M+1).

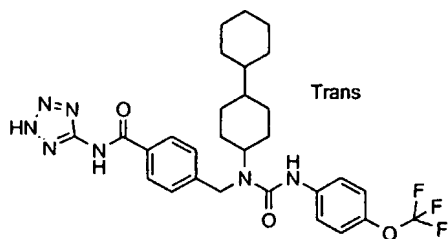
To a solution of the above benzoic acid (192 mg, 0.36 mmol) in DMF (10 mL) was added diisopropylethylamine (0.19 mL, 137 mg, 0.72 mmol) and HBTU (190 mg, 0.51 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (74 mg, 0.72 mmol) was added. After stirring for 16 hours, the solvent was evaporated, the residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄), and concentrated. The residue was purified by HPLC to afford the title compound.

¹H NMR (DMSO-*d*₆): δ 0.66 - 1.80 (m, 20H), 4.10 (m, 1H), 4.65 (s, 2H), 7.23 (d, 2H), 7.43 (d, 2H), 7.54 (d, 2H), 8.05 (d, 2H), 8.58 (s, 1H), 12.26 (s, 1H).

MS (APCI, pos.): 586.1 (M+1).

EXAMPLE 576

4-[1-(4-*trans*-Cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



To a solution of methyl 4-[4-(*trans*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate (338 mg, 1.03 mmol) in dichloromethane (8 mL) was added at room temperature 4-(trifluoromethoxy)-phenylisocyanate (210 mg, 1.03 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with dichloromethane (10 mL), washed with 1N HCl (5 mL), brine (5 mL), dried (MgSO₄), and concentrated. After flash chromatography (hexanes, ethyl acetate, 5:1), 487 mg of 4-[1-(4-*trans*-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoic acid methyl ester was obtained.

¹H NMR (CDCl₃): δ 0.91 - 1.41 (m, 12H), 1.61 - 1.90 (m, 8H), 3.93 (s, 3H), 4.19 (m, 1H), 4.55 (s, 2H), 6.18 (s, 1H), 7.07 (d, 2H), 7.20 (d, 2H), 7.45 (d, 2H), 8.06 (d, 2H).

eluted with hexane, ethyl acetate, 5:1, the *trans*-isomer (338 mg) eluted with hexane, ethyl acetate, 1:1.

Methyl 4-[4-(*cis*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate:

- 5 ¹H NMR (CDCl₃): δ 0.91 - 1.75 (m, 20H), 2.75 (m, 1H), 3.82 (s, 2H), 3.91 (s, 3H), 7.41 (d, 2H), 8.00 (d, 2H).

MS (APCI, pos.): 330.2 (M+1).

- 10 Methyl 4-[4-(*trans*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate:

¹H NMR (CDCl₃): δ 0.87 - 1.20 (m, 11H), 1.59 - 1.72 (m, 7H), 1.83 (d, 2H), 2.36 (m, 1H), 3.80 (s, 2H), 3.87 (s, 3H), 7.33 (d, 2H), 7.95 (d, 2H).

MS (APCI, pos.): 330.2 (M+1).

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To a solution of methyl 4-[4-(*cis*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate (340 mg, 1.03 mmol) in dichloromethane (8 mL) was added 4-(trifluoromethoxy)phenylisocyanate (210 mg, 1.03 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with dichloromethane (10 mL), washed with 1N HCl (5 mL), brine (5 mL), dried (MgSO₄), and concentrated. Recrystallisation from hexanes, ethyl acetate 1:1 provided 290 mg of 4-[1-(4-*cis*-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester.

20

¹H NMR (CDCl₃): δ 0.79 - 1.95 (m, 20H), 3.93 (s, 3H), 4.48 (m, 1H), 4.55 (s, 2H), 6.15 (s, 1H), 7.07 (d, 2H), 7.20 (d, 2H), 7.45 (d, 2H), 8.08 (d, 2H).

25

MS (APCI, pos.): 533.2 (M+1).

The above ester (290 mg, 0.54 mmol) was dissolved in THF (5 mL) and methanol (5 mL) and 1M KOH (2 mL) was added. The mixture was refluxed for 1 hour, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue crystallized from hexane, ethyl acetate to afford 192 mg of 4-[1-(4-*cis*-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid as a white solid.

30

¹H NMR (CD₃OD): δ 0.87 - 1.36 (m, 11H), 1.59 - 1.72 (m, 7H), 1.73 (d, 2H), 2.41 (m, 1H), 3.64 (s, 4H), 4.11 (s, 1H), 7.17 (d, 2H), 7.35 (d, 2H), 7.44 (d, 2H), 7.87 (d, 2H).

MS (APCI, pos.): 490.2.2 (M+1).

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To a suspension of above benzoic acid (215 mg, 0.44 mmol) in DMF (10 mL) was added diisopropylethylamine (0.23 mL, 166 mg, 1.28 mmol) and HBTU (200 mg, 0.53 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (180 mg, 1.75 mmol) was added to the solution. After stirring for 16 hours, the solvent was evaporated. The residue was dissolved in ethyl acetate (30 mL), washed with water (3 x 10 mL), and brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography (CHCl₃, methanol, 95:5) gave 110 mg of the title compound, which was further purified by HPLC.

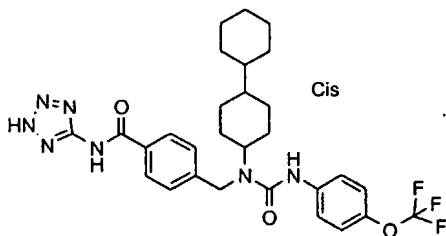
¹H NMR (CD₃OD): δ 0.98 - 1.27 (m, 9H), 1.64 - 1.85 (m, 7H), 1.93 (m, 2H), 2.14 (m, 2H), 3.23 (m, 1H), 4.52 (m, 4H), 7.36 (d, 2H), 7.53 (d, 2H), 7.60 (d, 2H), 8.10 (d, 2H).

15

MS (APCI, pos.): 557.3 (M+1).

EXAMPLE 575

20 4-[1-(4-*cis*-Cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



To a suspension of methyl 4-(aminomethyl)benzoate hydrochloride (2.0 g, 10 mmol) (prepared according to P. M. O'Brien et al., J. Med. Chem. 37, 1994, 1810-22) in ethanol (150 mL) was added 4-(4-cyclohexyl)cyclohexanone (1.8 g, 10 mmol) and NaBH(OAc)₃ (2.7 g, 12 mmol). The mixture was stirred for 16 hours at room temperature, and filtered by suction. The filtrate was concentrated, and the residue was dissolved in ethyl acetate (150 mL), washed with NaHCO₃ solution (100 mL), brine (100 mL), dried (Na₂SO₄), and concentrated. *Cis*- and *trans*-isomers were separated by flash chromatography. The *cis*-isomer (340 mg)

30

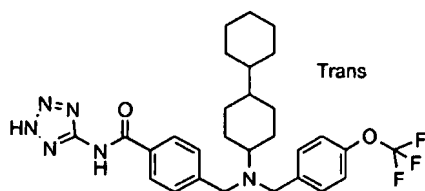
¹H NMR (DMSO-*d*₆): δ 0.75 - 1.80 (m, 20H), 2.45 (m, 1H), 3.63 (s, 2H), 3.65 (s, 2H), 4.67 (d, 2H), 7.28 (d, 2H), 7.43 (d, 2H), 7.46 (d, 2H), 7.82 (d, 2H), 8.96 (t, 1H).

MS (APCI, pos.): 571.2 (M+1).

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EXAMPLE 574

4-(((*trans*-4-Cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



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To a solution of *trans*-*N*-4-(4-cyclohexylcyclohexyl)-4-trifluoromethoxybenzylamine (350 mg, 0.98 mmol) in dichloromethane was added methyl 4-formylbenzoate (160 mg, 0.98 mmol) and NaBH(OAc)₃ (310 mg, 1.47 mmol). The mixture was stirred at room temperature for 16 hours. Additional aldehyde (160 mg) and NaBH(OAc)₃ (360 mg) were added. Stirring was continued for 72 hours at room temperature. The mixture was diluted with ethyl acetate (20 mL), washed with NaHCO₃ solution (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated. Flash chromatography (hexanes, ethyl acetate, 5:1) provided methyl 4-(((4-*trans*-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)benzoate (290 mg).

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¹H NMR (CDCl₃): δ 0.88 - 1.31 (m, 11H), 1.59 - 1.72 (m, 7H), 1.88 (d, 2H), 2.39 (m, 1H), 3.61 (s, 2H), 3.66 (s, 2H), 3.90 (s, 3H), 7.11 (d, 2H), 7.35 (d, 2H), 7.41 (d, 2H), 7.95 (d, 2H).

20

MS (APCI, pos.): 504.2 (M+1).

The above methyl benzoate (290 mg, 0.57 mmol) was dissolved in THF (5 mL) and methanol (5 mL) and 1M KOH (2 mL) were added. The mixture was refluxed for 90 minutes, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue crystallized from hexanes, ethyl acetate to afford 4-(((4-*trans*-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)benzoic acid (252 mg) as a white solid.

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¹H NMR (CD₃OD): δ 0.70 (m, 2 H), 1.13- 1.22 (m, 8H), 1.61-2.00 (m, 10H), 3.38 (t, 1H), 4.26 (m, 2H), 4.54 (m, 2H), 7.34 (d, 2H), 7.67 (d, 2H), 7.75 (d, 2H), 7.87 (d, 2H). MS (APCI, pos.): 490.2 (M+1).

5

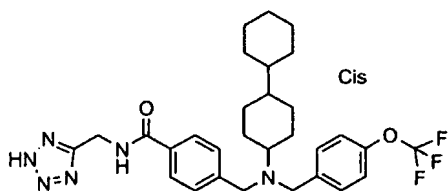
To a solution of above benzoic acid (250 mg, 0.51 mmol) in DMF (8 mL) was added diisopropylethylamine (0.18 mL, 130 mg, 0.61 mmol) and HBTU (228 mg, 0.61 mmol). After stirring for 15 min at room temperature, 5-aminotetrazole (105 mg, 1.01 mmol) was added. The mixture was stirred for 16 hours, and the solvent was evaporated. The residue was dissolved
10 in ethyl acetate (20 mL), washed with water (2 x 10 mL), and brine (10 mL), dried (MgSO₄), and concentrated. The residue was dissolved in dichloromethane. On addition of ether and hexane, the title compound crystallized. Yield: 26 mg.

¹H NMR (DMSO-*d*₆): δ 0.70 - 0.84 (m, 2H), 1.00- 1.80 (m, 18H), 2.40 (m, 1 H), 3.65 (s, 2H),
15 3.70 (s, 2H), 7.27 (d, 2H), 7.46 (d, 2H), 7.50 (d, 2 H), 8.01 (d, 2H).

MS (APCI, pos.): 557.2 (M+1).

EXAMPLE 573

20 4-(((4-*cis*-Cyclohexyl)cyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)methyl)benzamide



To a solution of the above 4-(((4-*cis*-cyclohexyl)cyclohexyl)-[4-(trifluoromethoxy)benzyl]-
25 amino)methyl)benzoic acid (242 mg, 0.49 mmol) in DMF (8 mL) was added diisopropylethylamine (0.18 mL, 130 mg, 0.61 mmol) and HBTU (220 mg, 0.59 mmol). After stirring for 15 minutes at room temperature, 5-aminomethyltetrazole (58 mg, 0.59 mmol) was added. The mixture was stirred for 16 hours, and the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), and brine (10 mL), dried
30 (MgSO₄), and concentrated. The residue was purified by HPLC to afford the title compound.

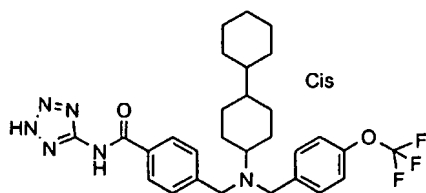
trated. The residue was dissolved in acetone (15 mL), filtered by suction, and the filtrate was concentrated. On addition of ethyl ether the title compound crystallized. Yield: 65 mg.

¹H NMR (DMSO-d₆, D₂O, NaOD): δ 0.80-1.82 (m, 20H), 2.13 (t, 2 H), 2.60 (t, 1H), 3.33 (t, 2H), 3.55 (s, 2H), 3.57 (s, 2H), 7.22 (d, 2H), 7.36 (d, 2H), 7.42 (d, 2H), 7.68 (d, 2H).

MS (APCI, pos.): 561.2 (M+1).

EXAMPLE 572

10 4-(((4-*cis*-Cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



To a solution of crude *cis*-*N*-4-(4-cyclohexylcyclohexyl)-4-trifluoromethoxybenzylamine (1.70g) in dichloromethane (10 mL) was added methyl 4-formylbenzoate (500 mg, 3.04 mmol) and NaBH(OAc)₃ (500 mg, 2.36 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with dichloromethane (20 mL), washed with NaHCO₃ solution (2 x 20 mL) and brine (20 mL), dried (MgSO₄), and concentrated. Flash chromatography (hexane, ethyl acetate, 9:1) provided methyl 4-(((4-*cis*-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)-benzyl]amino)methyl)benzoate (836 mg).

¹H NMR (CDCl₃): δ 0.77 - 1.85 (m, 20H), 2.50 (m, 1H), 3.62 (s, 2 H), 3.68 (s, 2 H), 3.90 (s, 3H), 7.11 (d, 2H), 7.35 (d, 2 H), 7.40 (d, 2H), 7.95 (d, 2H).

25 MS (APCI, pos.): 504.2 (M+1).

The above ester (836 mg, 1.66 mmol) was dissolved in THF (10 mL) and methanol (10 mL), and 1M KOH (4 mL) was added. The mixture was refluxed for 5h, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue crystallized from hexanes and ethyl acetate. Yield: 786 mg of 4-(((4-*cis*-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]-amino)methyl)benzoic acid as a white solid.

The above ester was dissolved in THF (10 mL), and 1M LiOH (0.5 mL) was added. After stirring at room temperature for 16 hours, the solution was acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in acetone (15 mL), filtered by suction, and the filtrate was concentrated. The title compound was purified by HPLC.

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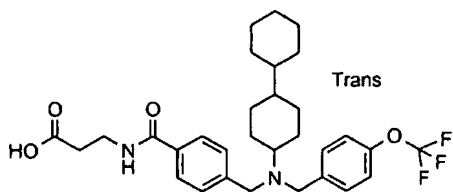
¹H NMR (DMSO-*d*₆): δ 0.71-1.87 (m, 20H), 2.37 (t, 2 H), 3.40 (t, 2H), 3.61 (s, 2H), 3.63 (s, 2H), 7.20 (d, 2H), 7.39 (d, 2 H), 7.44 (d, 2H), 7.67 (d, 2H), 8.53 (t, 1H).

MS (APCI, pos.): 561.3 (M+1).

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EXAMPLE 571

3-(4-[(trans-4-Cyclohexylcyclohexyl)-(4-trifluoromethoxybenzyl)amino]methyl)benzoyl-amino)propionic acid



15

To a solution of *N*-[4-(trans-4-cyclohexylcyclohexyl)]-4-trifluoromethoxybenzylamine (149 mg, 0.42 mmol) in dichloromethane (10-mL) was added ethyl 3-[(4-formylbenzoyl) amino] propionate (104 mg, 0.42 mmol) and NaBH(OAc)₃ (132 mg, 0.62 mmol). After stirring for 16 hours at room temp. additional aldehyde (100 mg) and NaBH(OAc)₃ (132 mg) were added. After stirring for 72 hours at room temp., the mixture was diluted with ethyl acetate (20 mL), washed with NaHCO₃ solution (10 mL), brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography (hexane, ethyl acetate, 3:1) provided the title compound (74.2 mg).

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¹H NMR (CDCl₃): δ 0.82 - 1.77 (m, 21H), 1.89 (d, 2H), 2.38 (tt, 1 H), 2.64 (t, 2H), 3.60 (s, 2H), 3.64 (s, 2H), 3.72 (q, 2H), 4.16 (q, 2H), 6.82 (t, 1H), 7.12 (d, 2H), 7.35 (d, 2H), 7.40 (d, 2H), 7.68 (d, 2H).

25

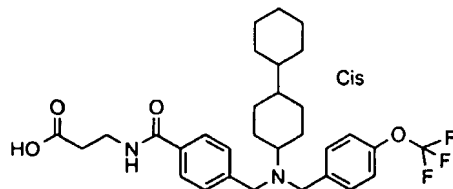
MS (APCI, pos.): 589.2 (M+1)

30

The above ester was dissolved in THF, and excess 1M LiOH was added. After stirring at room temperature for 16 hours, the solution was acidified with 1N HCl to pH=4, and concen-

EXAMPLE 570

3-(4-[[*cis*-4-Cyclohexylcyclohexyl)-(4-trifluoromethoxybenzyl)amino]methyl]benzoylamino)-propionic acid



5

To a solution of 4-trifluoromethoxybenzylamine (2.76 g, 14.4 mmol) in methanol (150 mL) was added 4-(4-cyclohexyl)cyclohexanone (2.60 g, 14.4 mmol) and NaBH(OAc)₃ (3.64 g, 17.2 mmol). The mixture was stirred for 16 hours at room temperature, and filtered by suction. The filtrate was concentrated, the residue was dissolved in ethyl acetate (150 mL), washed with NaHCO₃ solution (100 mL), brine (100 mL), dried (Na₂SO₄), and concentrated. The *cis*- and *trans*-isomers were separated by flash chromatography. The *cis*-isomer together with a byproduct eluted with hexane, ethyl acetate (5:1) and was used without further purification and characterization in the next step. Pure *trans*-isomer was eluted with hexane, ethyl acetate (3:1).

15

N-[4-(*trans*-4-Cyclohexyl)cyclohexyl]-4-trifluoromethoxybenzylamine:

¹H NMR (CDCl₃): δ 0.82- 1.17 (m, 11H), 1.59 - 1.76 (m, 7H), 1.86 (d, 2H), 2.41 (m, 1H), 3.81 (s, 2 H), 7.16 (d, 2H), 7.34 (d, 2H). MS (APCI, pos.): 356.2 (M+1).

To a solution of crude *N*-4-(*cis*-4-cyclohexylcyclohexyl)-4-trifluoromethoxybenzylamine (760 mg) in dichloromethane (10 mL) was added ethyl 3-[(4-formylbenzoyl)amino]propionate (240 mg, 1.0 mmol) and NaBH(OAc)₃ (240 mg, 1.1 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with ethyl acetate (20 mL), washed with NaHCO₃ solution (10 mL), and brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography (hexane, ethyl acetate, 3:1) afforded *N*-[4-[(*cis*-4-cyclohexyl)cyclohexyl]]-[4-(trifluoromethoxy)benzyl]amino}methyl]benzoyl]-β-alanine ethyl ester (226 mg).

25

¹H NMR (CDCl₃): δ 0.82 - 1.86 (m, 23H), 2.49 (m, 1H), 2.64 (t, 2H), 3.62 (s, 2H), 3.66 (s, 2H), 3.70 (q, 2H), 4.15 (q, 2 H), 6.84 (t, 1H), 7.12 (d, 2H), 7.35 (d, 2H), 7.40 (d, 2H), 7.68 (d, 2H).

30 MS (APCI, pos.): 589.2 (M+1)

solved in THF (2 mL) and a solution of tetrabutylammonium fluoride in THF (0,4 mL, 0,4 mmol, 1M) was added. The mixture was stirred for 6.5 hours and concentrated in vacuo. The residue was purified by column chromatography using 35 g of silica and dichloromethane and 10% ammonia in ethanol (80:20) as eluent to give 75 mg of the title compound.

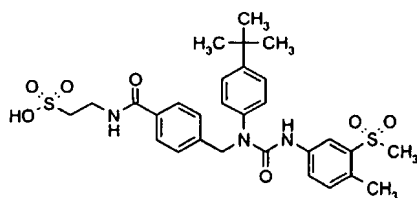
- 5 ¹H NMR (DMSO-*d*₆): δ 1.52-1.62 (6H, m), 1.68-1.83 (5H, m), 4.50 (2H, d), 4.98 (2H, s), 5.36 (1H, t), 7.16-7.22 (5H, m), 7.40 (2H, d), 7.53 (1H, dd), 7.64 (1H, d), 7.95 (2H, d), 8.44 (1H, s), 10.67 (1H, broad)

HPLC ms (method B): m/z: 610, R_t = 7.34 min.

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EXAMPLE 569

2-{4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonyl-4-methylphenyl)ureidomethyl]-benzoylamino}-ethanesulfonic acid



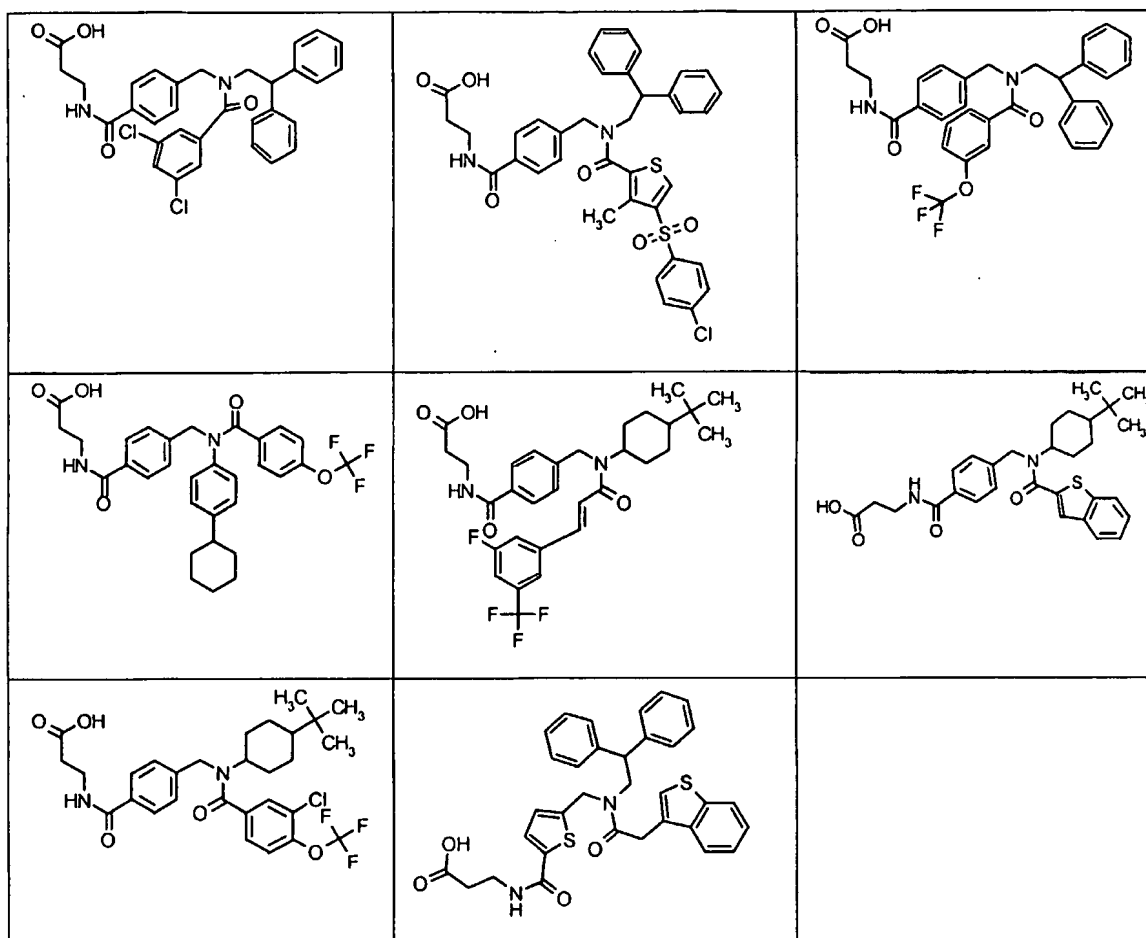
15

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonyl-4-methylphenyl)ureidomethyl]benzoic acid (300 mg, 0.6 mmol) was dissolved in DMF (10 ml). Hydroxybenzotriazole (100 mg, 0.7 mmol), and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (130 mg, 0.7 mmol) were added and the mixture was stirred for 30 minutes at room temperature followed by addition of
 20 2-aminoethanesulfonic acid (110 mg, 0.9 mmol) and diisopropylethylamine (120 mg, 160 μl, 1.0 mmol). After 16 hours the reaction mixture was poured into water (40 mL), pH was adjusted to acidic reaction with sodium hydrogen sulphate and the solution was concentrated in vacuo. The residue was purified by flash chromatography (20 g Silica Gel) using methanol and dichloromethane (10:90) as eluent to give 0.2 g of the title compound.

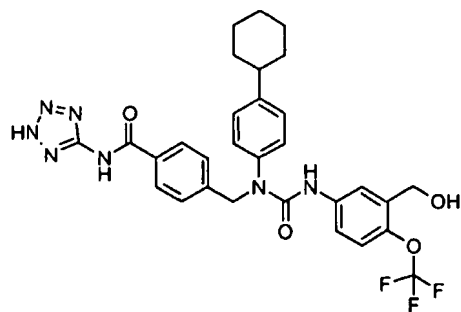
25

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.60 (s, 1H); 8.48 (t, 1H); 8.05 (s, 1H) 7.78 (d, 1H); 7.71 (d, 2H); 7.38 (d, 2H); 7.36 (d, 2H); 7.31 (d, 1H); 7.18 (d, 2H); 4.95 (s, 2H); 3.5 (q, 2H); 3.17 (s, 3H); 2.66 (t, 2H); 2.54 (s, 3H); 1.27 (s, 9H).

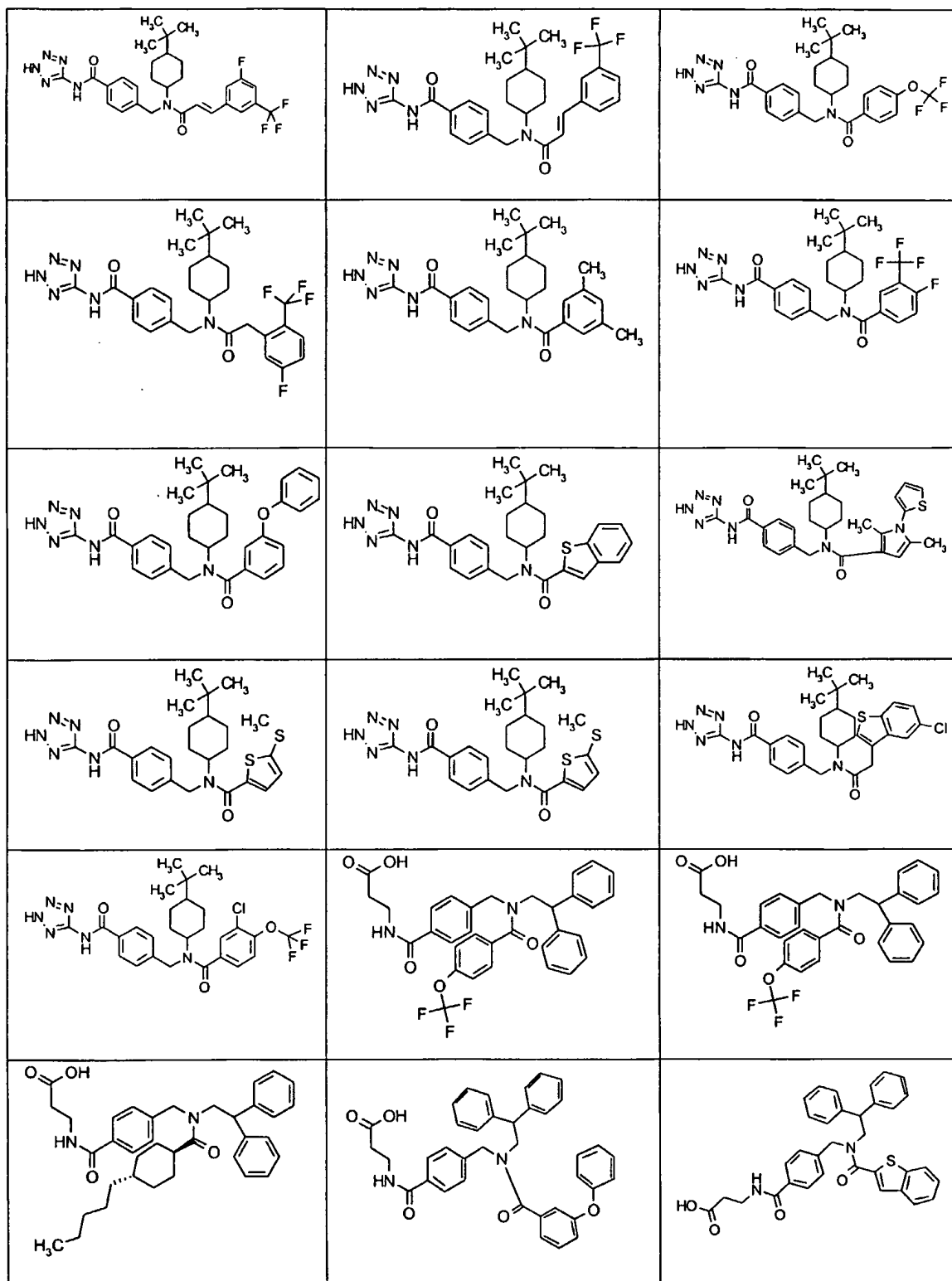
- 30 HPLC-MS (method B): m/z: 602, R_t = 4.8 min.

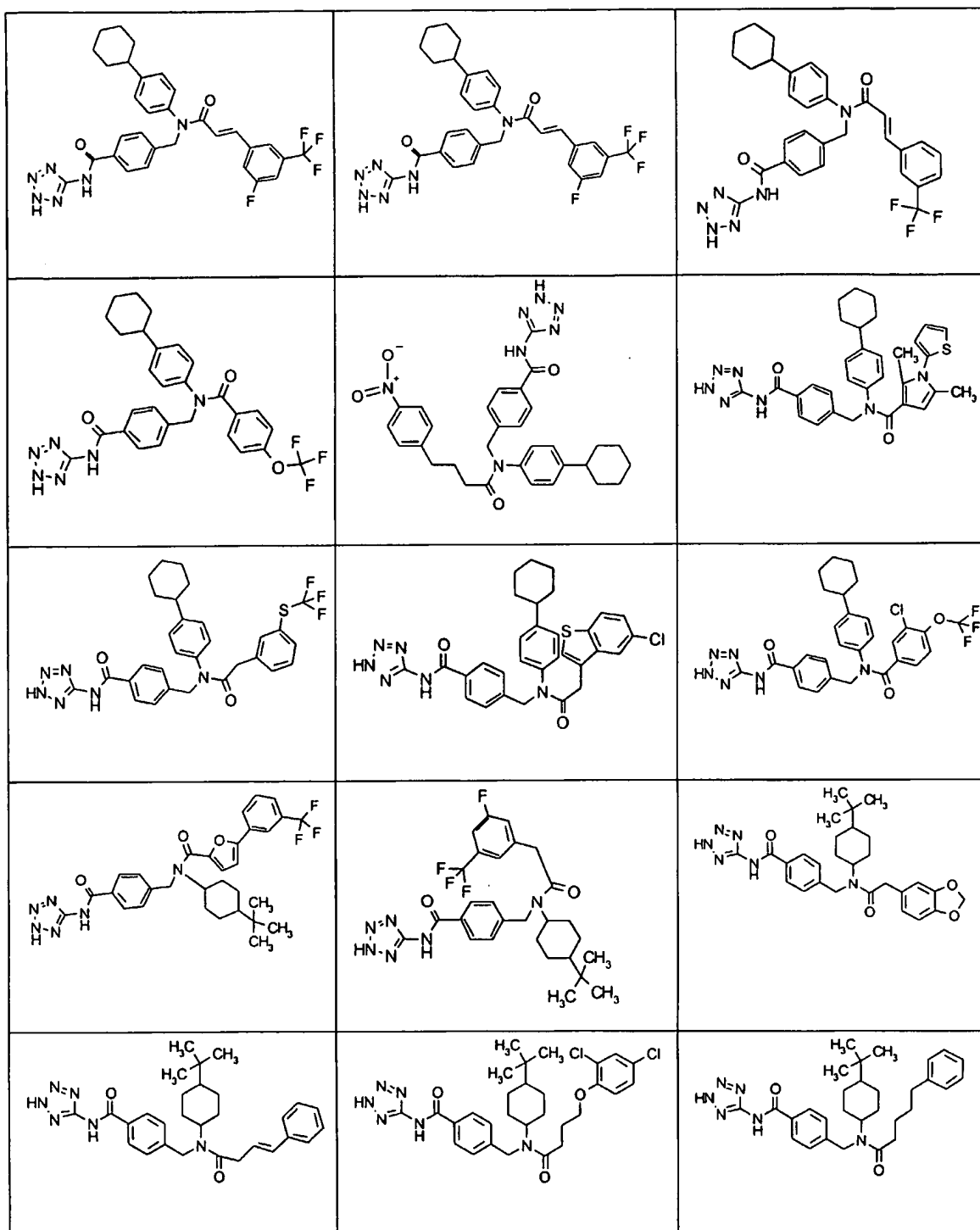
**EXAMPLE 568**

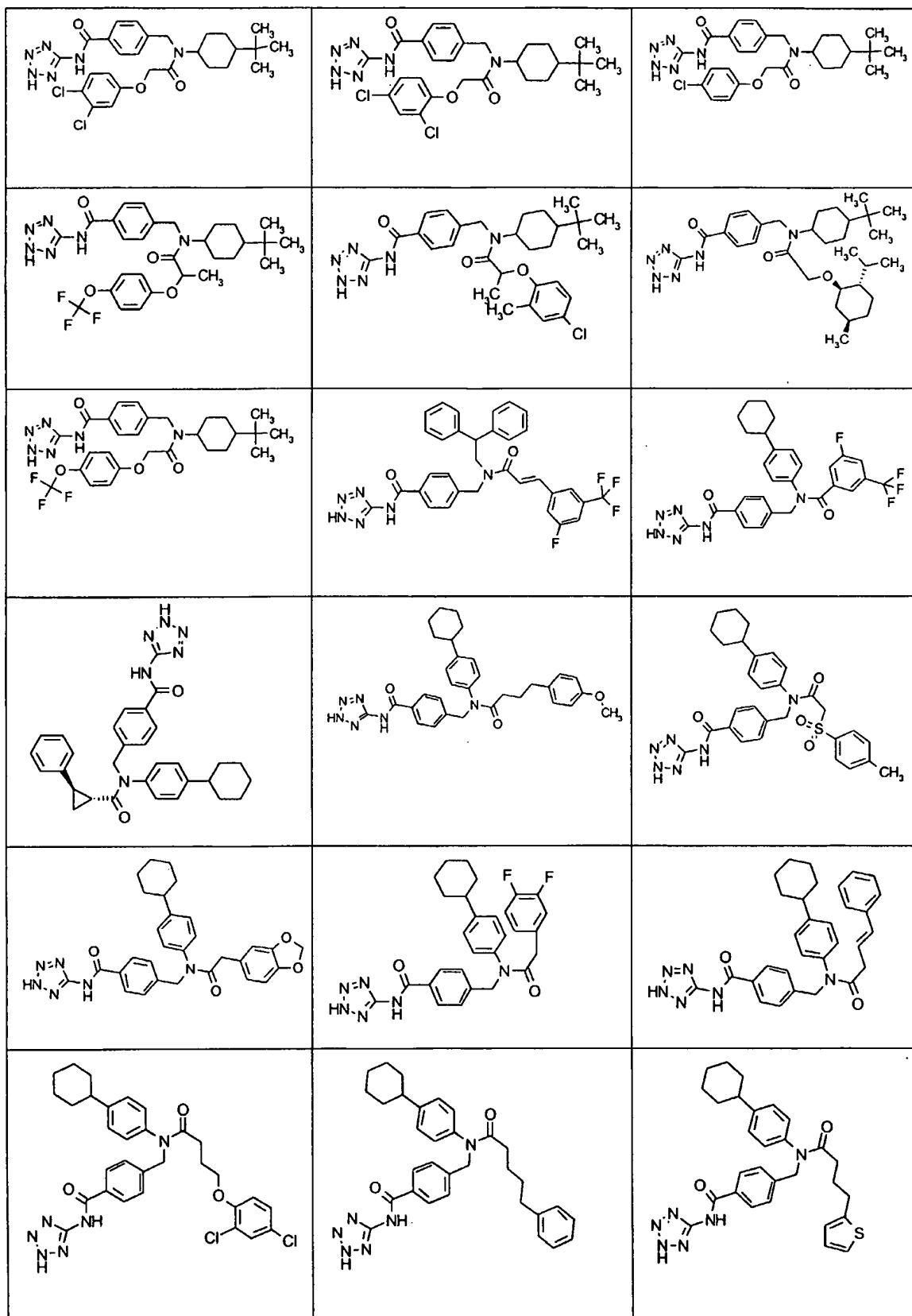
4-[1-(4-Cyclohexylphenyl)-3-(3-hydroxymethyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

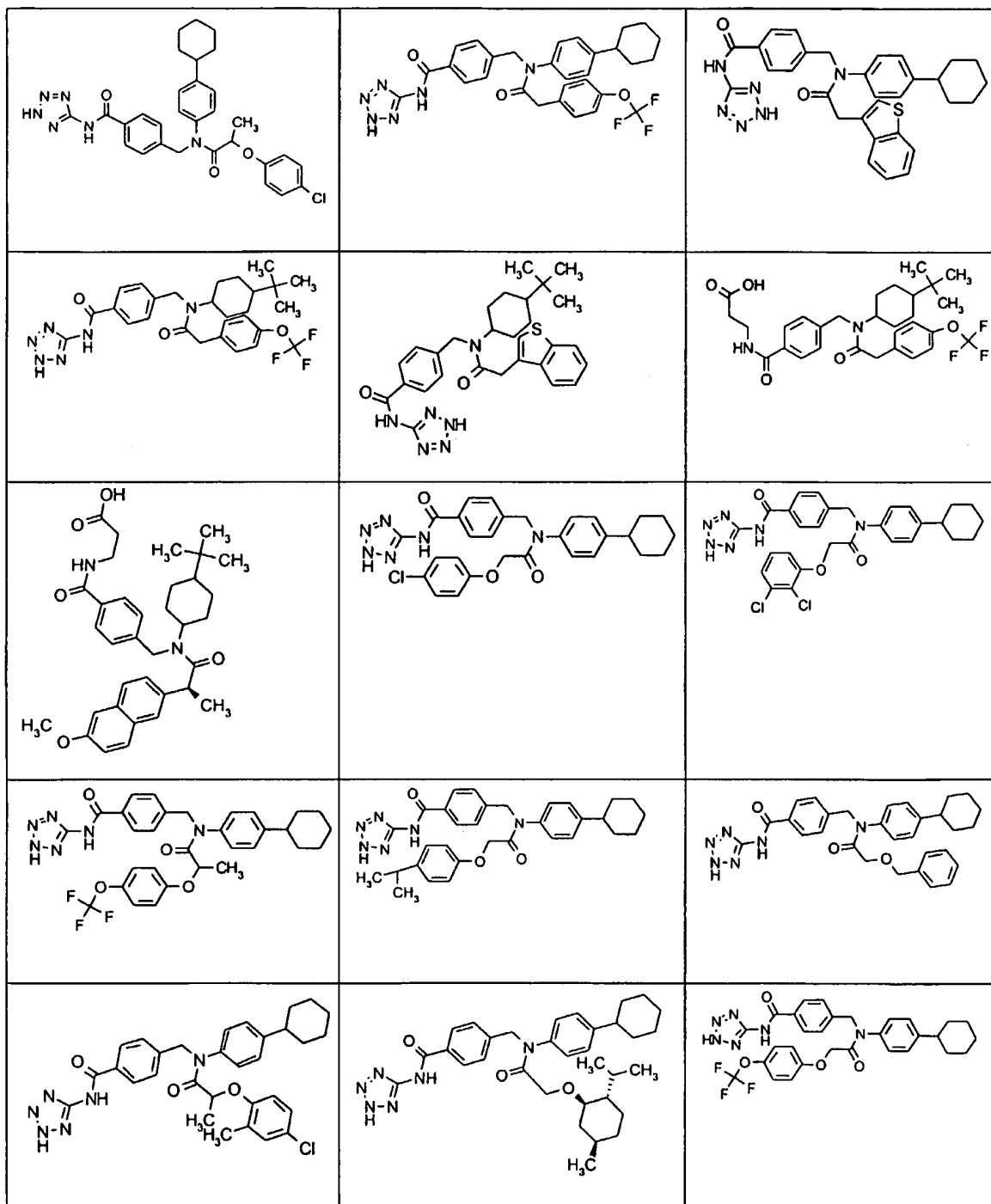


4-[3-[3-*tert*-Butyldimethylsilanyloxymethyl]-4-trifluoromethoxyphenyl]-1-(4-cyclohexylphenyl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide (0.09 g, 0.12 mmol) (example 293) was dis-



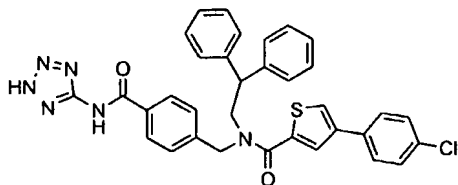






EXAMPLE 566 (general procedure (V))

4-(4-Chlorophenyl)thiophene-2-carboxylic acid (2,2-diphenyl-ethyl)-[4-(2H-tetrazol-5-yl-carbamoyl)benzyl]amide



5

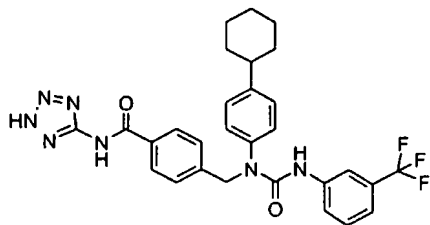
^1H NMR (DMSO- d_6): δ 12.44 (s, 1H); 8.10 (s+d, 3H); 7.60 (d, 2H); 7.45-7.15 (m, 15H); 4.62 (s, 2H); 4.59 (s br, 1H); 4.28 (br s, 2H).

HPLC-MS (Method B): m/z = 619 (M+1). R_t = 7.67 min.

10

EXAMPLE 567 (general procedure (V))

4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



15

^1H NMR (DMSO- d_6): δ 12.30 (s, 1H); 8.60 (s, 1H); 8.03 (d, 2H); 7.88 (s, 1H); 7.72 (d, 1H); 7.48 (m, 3H); 7.38 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.65 (m, 5H); 1.50-1.20 (m, 5H).

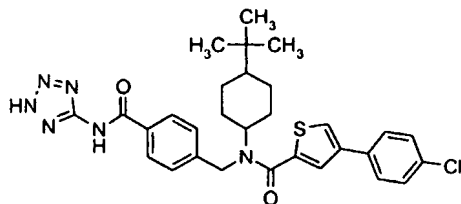
HPLC-MS (Method B): m/z = 564 (M+1), R_t = 7.85 min.

20

The following library of compounds was made according to general procedure (V). All of the compounds are expected to be present in the library.

EXAMPLE 564 (general procedure (V))

4-(4-Chlorophenyl)thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-yl-carbamoyl)benzyl]amide



5

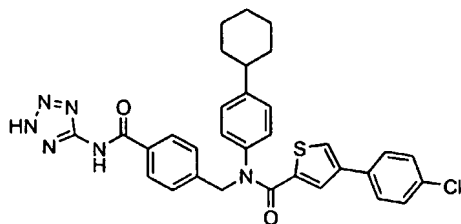
¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.10 (m, 3H); 7.85-7.65 (m, 3H); 7.50 (m, 4H); 4.85 (br d, 2H); 4.42+4.18 (m br, 1H); 1.95-1.48 (m, 7H); 1.20-1.00 (m, 2H); 0.80 (s, 9H).

HPLC-MS (Method B): *m/z* = 577 (M+1). *R*_t = 8.37 min.

10

EXAMPLE 565 (general procedure (V))

4-(4-Chlorophenyl)thiophene-2-carboxylic acid (4-cyclohexylphenyl)-[4-(2*H*-tetrazol-5-yl-carbamoyl)benzyl]amide



15

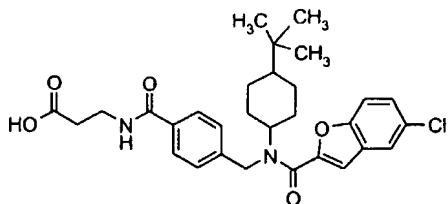
¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.05 (d+s, 3H); 7.52 (d, 2H); 7.35 (s, 4H); 7.28 (d, 2H); 7.18 (d, 2H); 6.61 (s, 1H); 5.11 (s, 2H); 1.90-1.65 (m, 5H); 1.60-1.15 (5H).

HPLC-MS (Method B): *m/z* = 597 (M+1). *R*_t = 8.65 min.

20

EXAMPLE 562 (general procedure (V))

3-(4-(((4-*tert*-Butylcyclohexyl)-(5-chlorobenzofuran-2-carbonyl)amino)methyl)benzoylamino)-propionic acid



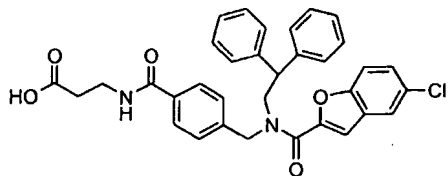
5

^1H NMR (DMSO- d_6): δ 12.25 (s, 1H); 8.52 (t, 1H); 7.92-7.70(m, 4H); 7.50-7.15 (m, 4H); 4.80 (d br, 2H); 4.25-4.00 (d br, 1H); 3.50 (dd, 2H); 1.90-1.50 (m, 6H); 1.10-0.90 (m, 3H); 0.75 (s, 9H).

10 HPLC-MS (Method B): m/z = 539 (M+1). R_t = 7.85 min.

EXAMPLE 563 (general procedure (V))

3-(4-(((5-Chlorobenzofuran-2-carbonyl)-(2,2-diphenylethyl)amino)methyl)benzoylamino)-propionic acid



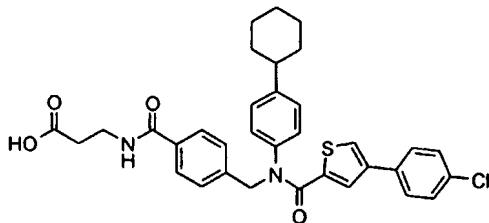
15

^1H NMR (DMSO- d_6): δ 8.52 (t, 1H); 7.80 (s, 3H); 7.58 (d, 1H); 7.50-7.05 (m, 14 H); 4.65 (s, 2H); 4.50-4.05 (m, 2H).

20 HPLC-MS (Method B): m/z = 581 (M+1). R_t = 7.17 min.

EXAMPLE 560 (general procedure (V))

3-(4-(((4-(4-Chlorophenyl)thiophene-2-carbonyl)-(4-cyclohexylphenyl)amino)methyl)-benzoylamino)propionic acid



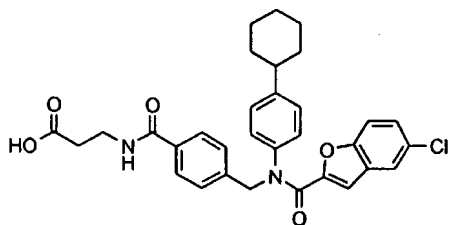
5

^1H NMR ($\text{DMSO}-d_6$): δ 12.25 (br s, 1H); 8.50 (t, 1H); 8.05 (s, 1H); 7.75 (d, 2H); 7.42-7.30 (m, 6H); 7.28 (d, 2H); 7.18 (d, 2H); 6.62 (s, 1H); 5.09 (s, 2H); 1.80-1.65 (m, 5H); 1.40-1.15 (m, 5H).

10 HPLC-MS (Method B): R_t = 8.32 min, m/z = 601 ($M+1$).

EXAMPLE 561 (general procedure (V))

3-(4-(((5-Chlorobenzofuran-2-carbonyl)-(4-cyclohexylphenyl)amino)methyl)benzoylamino)-propionic acid



15

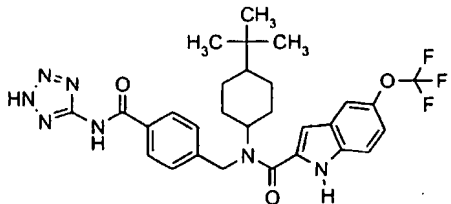
^1H NMR ($\text{DMSO}-d_6$): δ 8.51 (t, 1H); 7.78 (d, 2H); 7.67 (s, 1H); 7.49 (d, 1H); 7.42-7.32 (m, 3H); 7.21 (d, 2H); 7.14 (d, 2H); 6.47 (s, 1H); 5.11 (s, 2H); 1.80-1.65 (m, 5H); 1.45-1.10 (m, 5H).

20

HPLC-MS (Method B): m/z = 559 ($M+1$), R_t = 7.88 min.

EXAMPLE 557 (general procedure (V))

5-Trifluoromethoxy-1H-indole-2-carboxylic acid (4-tert-butylcyclohexyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]amide



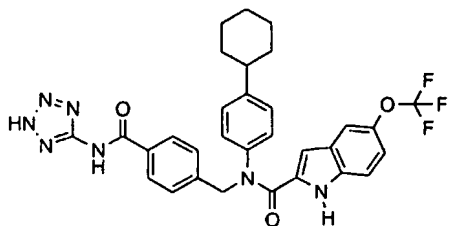
5

HPLC-MS (Method C): m/z = 584 ($M+1$), R_t = 8.07 min.

EXAMPLE 558 (general procedure (V))

5-Trifluoromethoxy-1H-indole-2-carboxylic acid (4-cyclohexylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]amide

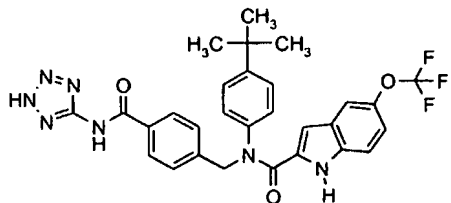
10



HPLC-MS (Method B): m/z = 604 ($M+1$), R_t = 8.33 min.

15 EXAMPLE 559 (general procedure (V))

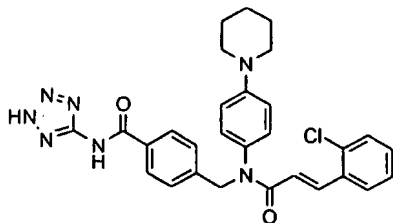
5-Trifluoromethoxy-1H-indole-2-carboxylic acid (4-tert-butylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]amide



20 HPLC-MS (Method B): m/z = 578 ($M+1$), R_t = 7.78 min.

EXAMPLE 555 (general procedure (V))

4-([3-(2-Chlorophenyl)acryloyl]-(4-piperidin-1-ylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

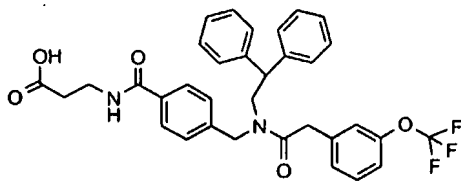
^1H NMR (DMSO): δ 8.13 (d, 2H); 7.95 (d, 1H); 7.60 (d, 1H); 7.54-7.45 (m, 5H); 7.15 (d, 2H); 7.01 (d, 2H); 6.58 (d, 1H); 5.13 (s, 2H).

HPLC-MS (Method D): m/z = 542 ($M+1$). R_t = 4.37 min.

10

EXAMPLE 556 (general procedure (V))

4-([2-(2,2-Diphenylethyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



15

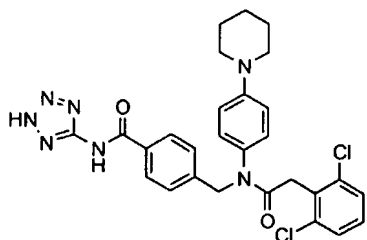
^1H NMR (DMSO) (isomers): δ 8.56 (t), 8.52 (t); 7.87 (d); 7.81 (d); 7.50-7.22 (m); 7.13 (s); 7.08 (t); 6.99 (s); 4.26 (s); 4.51 (q); 4.43 (s); 4.07 (d); 4.02 (d).

HPLC-MS (Method D): m/z = 605 ($M+1$). R_t = 5.37 min.

20

EXAMPLE 553 (general procedure (V))

4-([2-(2,6-Dichlorophenyl)acetyl]-(4-piperidin-1-ylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

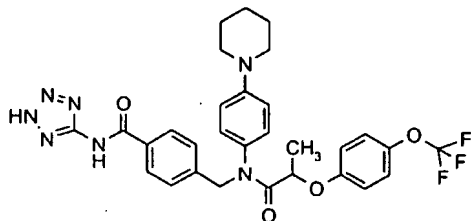
¹H NMR (DMSO): δ 8.13 (d, 2H); 7.48 (d, 2H); 7.41-7.36 (m, 2H); 7.34-7.30 (m, 3H); 7.05 (d, 2H); 6.93 (d, 2H); 5.00 (s, 2H).

HPLC-MS (Method D): m/z = 479 (M+1). R_t = 564 min.

10

EXAMPLE 554 (general procedure (V))

4-([2-(4-trifluoromethoxyphenoxy)propionyl]-(4-piperidin-1-ylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



15

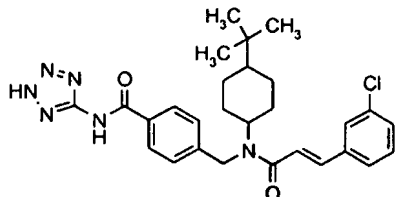
¹H NMR (DMSO): δ 8.10 (d, 2H); 7.40 (d, 2H); 7.36 (d, 2H); 7.13 (d, 2H); 6.95 (d, 2H); 6.90 (d, 2H); 5.05 (d, 1H); 4.95 (d, 1H); 4.80 (q, 1H).

HPLC-MS (Method D): m/z = 610 (M+1). R_t = 4.83 min.

20

EXAMPLE 551 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[3-(3-chlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

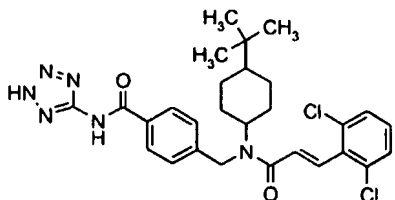
¹H NMR (DMSO) (isomers): δ 8.15 (d) 8.11 8(d) 8.00 (s); 7.85-7.75 (m); 7.70-7.40 (m); 7.11 (d); 5.05 (s); 4.85 (s).

HPLC-MS (Method D): m/z = 521 (M+1). R_t = 6.03 min.

10

EXAMPLE 552 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



15

¹H NMR (DMSO): δ 8.16 (d); 8.13 (d); 7.70-7.30 (m); 6.84 (d)

HPLC-MS (Method D): m/z = 555 (M+1). R_t = 6.23 min.

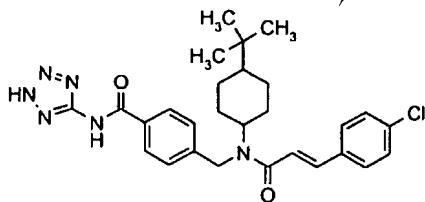
^1H NMR (DMSO): δ 8.05 (d, 2H); 7.44 (t, 1H); 7.34 (d, 2H); 7.13 (d, 1H); 7.10 (s, 1H); 7.01 (d, 1H); 5.70 (q, 1H); 4.60-4.70 (dd, 2H).

HPLC-MS (Method D): m/z = 539 ($M+1$). R_t = 5.97 min.

5

EXAMPLE 549 (general procedure (V))

4-((4-*tert*-Butylcyclohexyl)-[3-(4-chlorophenyl)acroyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



10

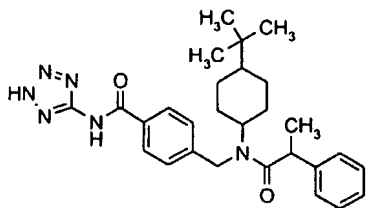
^1H NMR (DMSO) (isomers): δ 8.15 (d); 8.11(d); 7.90 (d); .7.70-7.62 (m); 7.58 (d); 7.55-7.42 (m); 7.03 (d); 5.15 (s); 5.00 (s).

HPLC-MS (Method D): m/z = 521 ($M+1$). R_t = 6.07 min.

15

EXAMPLE 550 (general procedure (V))

4-[[4-(4-*tert*-Butylcyclohexyl)-(2-phenylpropionyl)amino]methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide

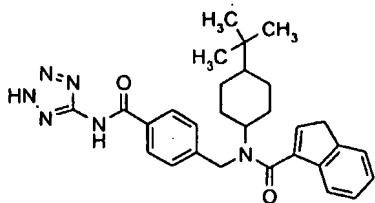


20 HPLC-MS (Method D): m/z = 489 ($M+1$). R_t = 5.83 min.

HPLC-MS (Method D): m/z = 503 ($M+1$). R_t = 5.97 min.

EXAMPLE 546 (general procedure (V))

- 5 4-((4-*tert*-Butylcyclohexyl)-(3*H*-indene-1-carbonyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

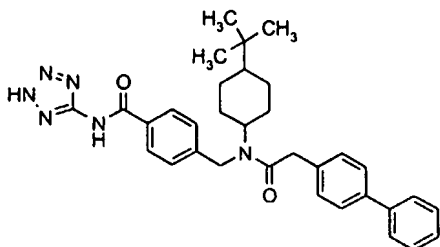


HPLC-MS (Method D): m/z = 499 ($M+1$). R_t = 5.67 min.

10

EXAMPLE 547 (general procedure (V))

- 4-((2-Biphenyl-4-ylacetyl)-(4-*tert*-butylcyclohexyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

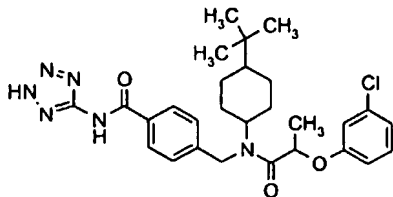


15

HPLC-MS (Method D): m/z = 551 ($M+1$). R_t = 6.27 min.

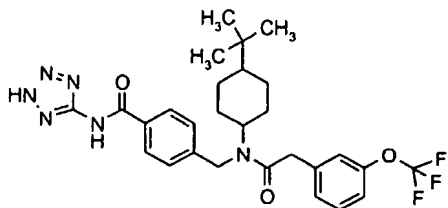
EXAMPLE 548 (general procedure (V))

- 20 4-((4-*tert*-Butylcyclohexyl)-[2-(3-chlorophenoxy)propionyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



EXAMPLE 543 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



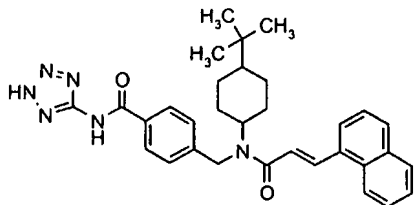
5

¹H NMR (DMSO) (isomers): δ 8.18-8.05 (two d, 2H); 7.60-7.15 (m, 6H); 4.90-4.60 (two s, 2H).

10 HPLC-MS (Method D): m/z = 559 (M+1). R_t = 6.03 min.

EXAMPLE 544 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-(3-naphthalen-1-yl-acryloyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

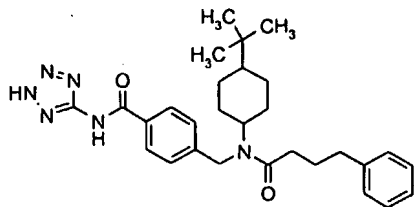


15

HPLC-MS (Method D): m/z = 537 (M+1). R_t = 6.23 min.

EXAMPLE 545 (general procedure (V))

20 4-(((4-*tert*-Butylcyclohexyl)-(4-phenylbutyryl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide

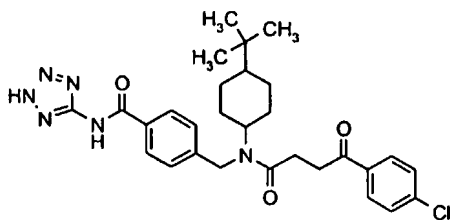


¹H NMR (DMSO) (isomers): δ 8.15, 8.11 (d, 2H); 7.45-7.15 (m, 7H); 4.68, 4.65 (s, 2H).

HPLC-MS (Method D): m/z = 543 ($M+1$). R_t = 6.20 min.

EXAMPLE 540 (general procedure (V))

- 5 4-(((4-*tert*-Butylcyclohexyl)-[4-(4-chlorophenyl)-4-oxobutyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide

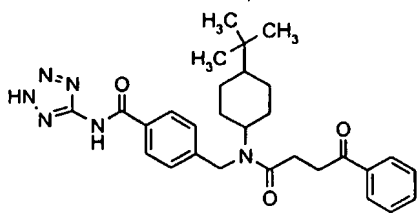


HPLC-MS (Method D): m/z = 551 ($M+1$). R_t = 5.93 min.

10

EXAMPLE 541 (general procedure (V))

- 4-(((4-*tert*-Butylcyclohexyl)-[4-oxo-4-phenylbutyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

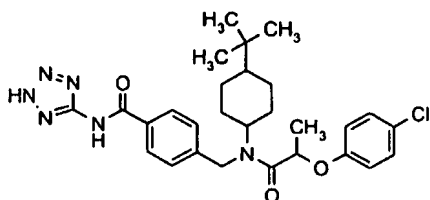


15

HPLC-MS (Method D): m/z = 515 ($M+1$). R_t = 5.60 min.

EXAMPLE 542 (general procedure (V))

- 20 4-(((4-*tert*-Butylcyclohexyl)-[2-(4-chlorophenoxy)propionyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

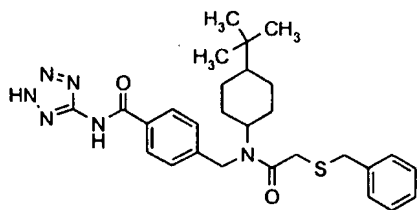


HPLC-MS (Method D): m/z = 539 ($M+1$). R_t = 5.97 min.

EXAMPLE 537 (general procedure (V))

4-(((2-Benzylsulfanylacetyl)-(4-*tert*-butylcyclohexyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

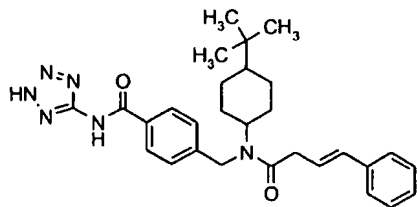
5



HPLC-MS (Method D): m/z = 521 ($M+1$). R_t = 5.87 min.

EXAMPLE 538 (general procedure (V))

10 4-(((4-*tert*-Butylcyclohexyl)-(4-phenylbut-3-enoyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

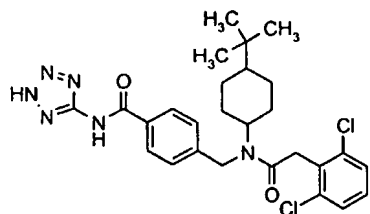


HPLC-MS (Method D): m/z = 501 ($M+1$). R_t = 5.83 min.

15

EXAMPLE 539 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[2-(2,6-dichlorophenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

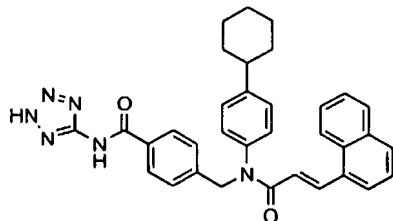


20

^1H NMR (DMSO) (molecule exists as isomers 1:2): Minor isomer: δ 8.22 (d, 2H); 4.94 (s, 2H); 3.96 (s, 2H). Major isomer: δ 8.10 (d, 2H); 4.68 (s, 2H); 4.30 (s, 2H). Both isomers: δ 7.70-7.30 (m).

EXAMPLE 534 (general procedure (V))

4-[[[(4-Cyclohexylphenyl)-(3-naphthalen-1-ylacryloyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

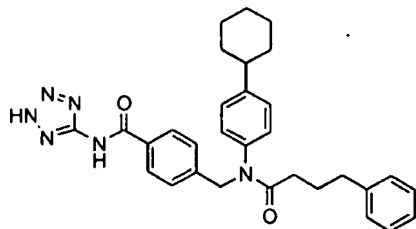


5

HPLC-MS (Method D): m/z = 557 ($M+1$). R_t = 6.50 min.

EXAMPLE 535 (general procedure (V))

4-[[[(4-Cyclohexylphenyl)-(4-phenylbutyryl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

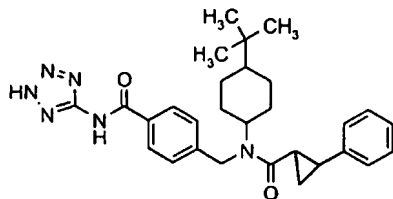


10

HPLC-MS (Method D): m/z = 523 ($M+1$). R_t = 6.13 min.

EXAMPLE 536 (general procedure (V))

15 4[[[(4-*tert*-Butylcyclohexyl)-(2-phenylcyclopropanecarbonyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide



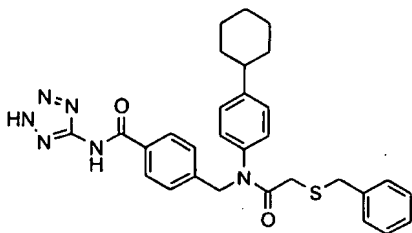
20

^1H NMR (DMSO): δ 8.09 (d, 2H); 8.04 (d, 2H); 7.44 (d, 4H); 7.40-7.10 (m, 8H); 7.01 (d, 2H); 4.92 (d, 1H); 4.77 (d, 1H); 4.72 (d, 1H); 4.68 (d, 1H); 4.44 (t, 1H); 4.13 (t, 1H).

HPLC-MS (Method D): m/z = 501 ($M+1$). R_t = 5.77 min.

EXAMPLE 532 (general procedure (V))

4-[[[(2-Benzylsulfanylacetyl)-(4-cyclohexylphenyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

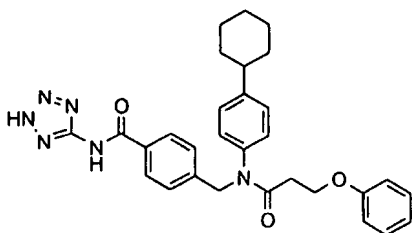


5

HPLC-MS (Method D): m/z = 541 ($M+1$). R_t = 6.03 min.

EXAMPLE 533 (general procedure (V))

10 4-[[[(4-Cyclohexylphenyl)-(3-phenoxypropionyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide



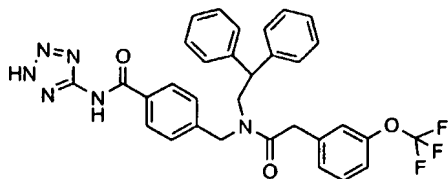
^1H NMR (DMSO): δ 8.11 (d, 2H); 7.51 (d, 2H); 7.39-7.30 (m, 3H); 7.26 (d, 2H); 7.03-6.97 (m, 4H); 5.20 (s, 2H); 4.25 (t, 2H).

15

HPLC-MS (Method D): m/z = 525 ($M+1$). R_t = 5.90 min.

EXAMPLE 529 (general procedure (V))

4-(((2,2-Diphenylethyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



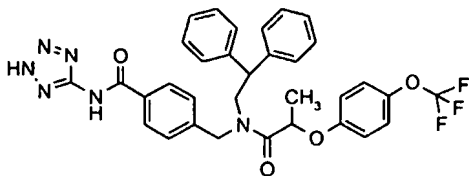
5

HPLC-MS (Method D): m/z = 601 ($M+1$). R_t = 5.60 min.

EXAMPLE 530 (general procedure (V))

4-(((2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenyl)propionyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide

10



^1H NMR (DMSO): δ 8.15 (d, 1H); 8.08 (d, 1H); 7.50-7.20 (m, 12H); 6.74 (d, 1H); 6.64 (d, 1H); 5.27 (q, 1H); 5.16 (q, 1H); 4.80 (d, 1H); (4.68 (d, 1H); 4.60-4.49 (m, 2H);

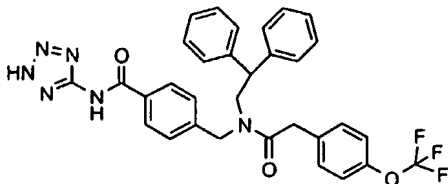
15

HPLC-MS (Method D): m/z = 631 ($M+1$). R_t = 5.63 min.

EXAMPLE 531 (general procedure (V))

4-(((2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide

20



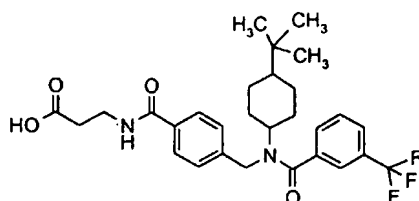
^1H NMR (DMSO): δ 8.13 (d, 1H); 8.08 (d, 1H); 7.50-7.28 (m, 14); 7.20 (d, 1H); 7.14 (d, 1H); 4.65 (s, 1H); 4.55 (t, 1H).

^1H NMR (DMSO): δ 8.52 (t, 1H); 7.82 (d, 2H); 7.45-7.37 (m, 4H); 7.07-6.97 (m, 2H).

HPLC-MS (Method D): m/z = 523 ($M+1$). R_t = 5.60 min.

5 EXAMPLE 527 (general procedure (V))

3-(4-(((4-*tert*-Butylcyclohexyl)-(3-trifluoromethylbenzoyl)amino)methyl)benzoylamino)propionic acid

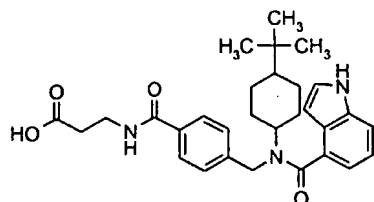


10 ^1H NMR (DMSO): δ 8.54 (s, 1H); 8.00-7.70 (m, 6H); 7.60-7.30 (m, 2H); 4.77 (s, 2H).

HPLC-MS (Method D): m/z = 533 ($M+1$). R_t = 5.53 min.

EXAMPLE 528 (general procedure (V))

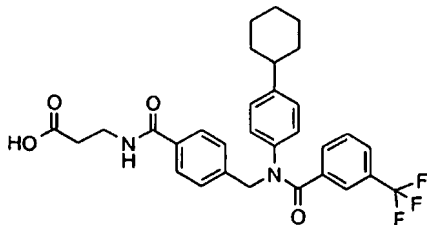
15 3-(4-(((4-*tert*-Butylcyclohexyl)-(1H-indole-4-carbonyl)amino)methyl)benzoylamino)propionic acid



HPLC-MS (Method D): m/z = 504 ($M+1$). R_t = 5.00 min.

EXAMPLE 524 (general procedure (V))

3-(4-{{(4-Cyclohexylphenyl)-(3-trifluoromethylbenzoyl)amino}methyl}benzoylamino)propionic acid



5

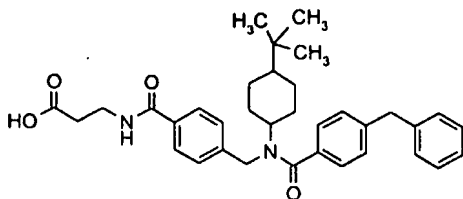
¹H NMR (DMSO): δ 8.54 (t, 1H); 7.82 (d, 2H); 7.75 (d, 1H); 7.70 (d, 1H); 7.56 (t, 1H); 7.53 (s, 1H); 7.46 (d, 2H); 7.10 (d, 2H); 7.07 (d, 2H); 5.20 (s, 2H).

HPLC-MS (Method D): m/z = 553 (M+1). R_t = 5.63 min.

10

EXAMPLE 525 (general procedure (V))

3-(4-{{(4-Benzylbenzoyl)-(4-tert-butylcyclohexyl)amino}methyl}benzoylamino)propionic acid

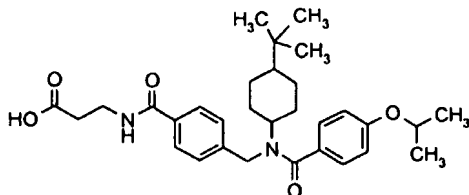


15 ¹H NMR (DMSO): δ 8.54 (t, 1H); 7.84 (d, 2H); 7.50-7.20 (m, 11H);

HPLC-MS (Method D): m/z = 555 (M+1). R_t = 6.00 min.

EXAMPLE 526 (general procedure (V))

20 3-(4-{{(4-tert-Butylcyclohexyl)-(4-isopropoxybenzoyl)amino}methyl}benzoylamino)propionic acid

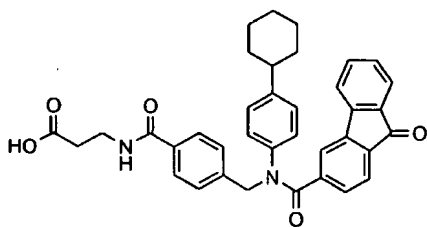


¹H NMR (DMSO): δ 8.53 (t, 1H); 7.82 (d, 2H); 7.42 (d, 2H); 7.33-7.20 (m, 9H); 7.08 (d, 2H); 7.00 (d, 2H); 5.10 (s, 2H).

HPLC-MS (Method D): m/z = 575 (M+1). R_t = 6.00 min.

5 EXAMPLE 522 (general procedure (V))

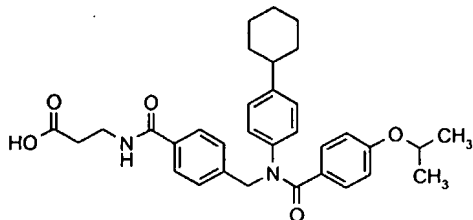
3-(4-(((4-Cyclohexylphenyl)-(9-oxo-9H-fluorene-3-carbonyl)amino)methyl)benzoylamino)-propionic acid



10 HPLC-MS (Method D): m/z = 587 (M+1). R_t = 5.40 min.

EXAMPLE 523 (general procedure (V))

3-(4-(((4-Cyclohexylphenyl)-(4-isopropoxybenzoyl)amino)methyl)benzoylamino)propionic acid

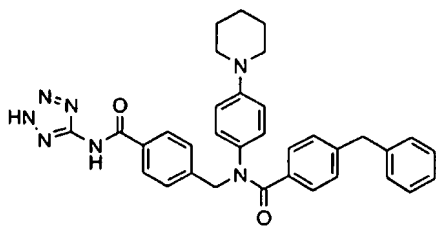


15

¹H NMR (DMSO): δ 8.52 (t, 1H); 7.78 (d, 2H); 7.40 (d, 2H); 7.27 (d, 2H); 7.09 (d, 2H); 7.00 (d, 2H); 6.76 (d, 2H); 5.15 (s, 2H).

HPLC-MS (Method D): m/z = 543 (M+1). R_t = 5.67 min.

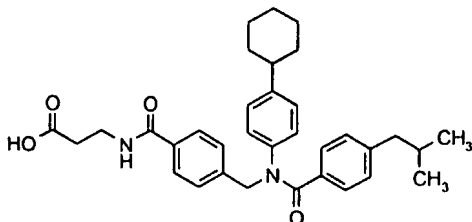
20

EXAMPLE 519 (general procedure (V))**4-[[[(4-Benzylbenzoyl)-(4-piperidin-1-ylphenyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide**

- 5 ¹H NMR (DMSO): δ 8.07 (d, 2H); 7.51 (d, 2H); 7.32-7.28 (m, 4H); 7.25-7.18 (m, 3H); 7.13 (d, 2H); 6.93 (d, 2H); 6.76 (d, 2H); 5.10 (s, 2H).

HPLC-MS (Method D): m/z = 572 (M+1). R_t = 4.17 min.

10 **EXAMPLE 520 (general procedure (V))**

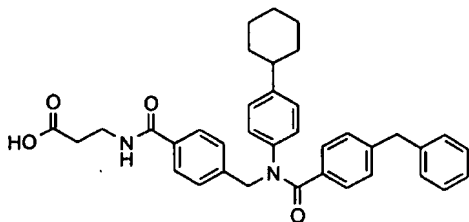
3-(4-[[[(4-Cyclohexylphenyl)-(4-isobutylbenzoyl)amino]methyl]benzoylamino]propionic acid

- 15 ¹H NMR (DMSO): δ 8.54 (t, 1H); 7.83 (d, 2H); 7.44 (d, 2H); 7.26 (d, 2H); 7.09-7.04 (m, 4H); 7.00 (d, 2H); 5.18 (s, 2H).

HPLC-MS (Method D): m/z = 541 (M+1). R_t = 6.17 min.

EXAMPLE 521 (general procedure (V))

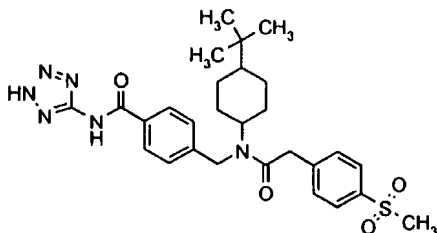
20 **3-(4-[[[(4-Benzylbenzoyl)-(4-cyclohexylphenyl)amino]methyl]benzoylamino]propionic acid**



HPLC-MS (Method D): m/z = 500 ($M+1$). R_t = 5.03 min.

EXAMPLE 517 (general procedure (V))

- 5 4-(((4-*tert*-Butylcyclohexyl)-[2-(4-methylsulfonylphenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



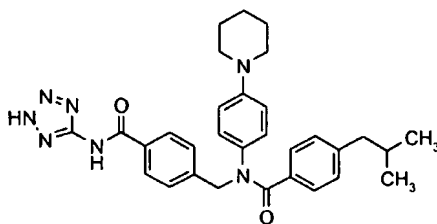
^1H NMR (DMSO. Isomers 2:1):

- 10 Set 1 (minor isomer): δ 8.16 (d, 2H); 7.88 (d, 2H); 7.52 (d, 2H); 7.47 (d, 2H); 4.80 (s, 2H).
Set 2 (major isomer): δ 8.06 (d, 2H); 7.96 (d, 2H); 7.64 (d, 2H); 7.42 (d, 2H); 4.70 (s, 2H).

HPLC-MS (Method D): m/z = 553 ($M+1$). R_t = 4.83 min.

- 15 EXAMPLE 518 (general procedure (V))

4-(((4-Isobutylbenzoyl)-(4-piperidin-1-ylphenyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide

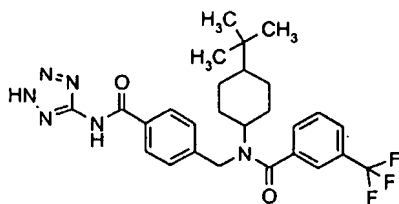


- 20 ^1H NMR (DMSO): δ 8.11 (d, 2H); 7.55 (d, 2H); 7.31 (d, 2H); 7.08 (d, 2H); 6.96 (d, 2H); 6.80 (d, 2H); 5.10 (s, 2H).

HPLC-MS (Method D): m/z = 538 ($M+1$). R_t = 4.23 min.

EXAMPLE 514 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-(3-trifluoromethylbenzoyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

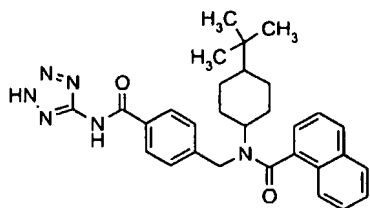
¹H NMR (DMSO): δ 8.11 (d, 2H); 8.00-7.70 (m, 3H); 7.65-7.40 (m, 3H); 4.70 (s, 2H).

HPLC-MS (Method D): m/z = 529 (M+1). R_t = 5.77 min.

10

EXAMPLE 515 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-(naphth-1-ylcarbonyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



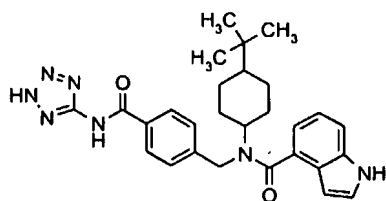
15

HPLC-MS (Method D): m/z = 511 (M+1). R_t = 5.77 min.

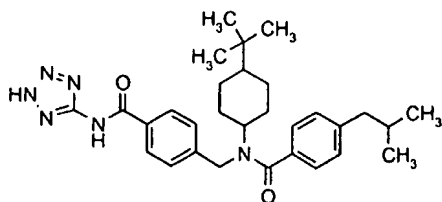
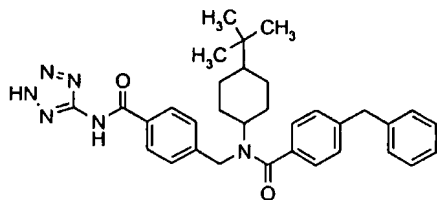
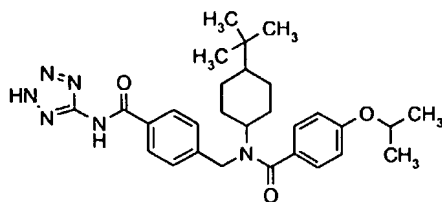
EXAMPLE 516 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-(1*H*-indol-4-ylcarbonyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

20



¹H NMR (DMSO): δ 8.20-8.05 (m, 2H); 7.70-7.60 (m, 1H); 7.60-7.45 (m, 3H); 7.28-7.12 (m, 1H); 7.08 (d, 1H); 6.40 (m, 1H); 4.70 (s br 2H).

EXAMPLE 511 (general procedure (V))**4-[[[(4-*tert*-Butylcyclohexyl)-(4-isobutylbenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**5 ¹H NMR (DMSO): δ 8.12 (d, 2H); 7.60-7.28 (m, 6H); 4.80 (m, 2H)HPLC-MS (Method D): m/z = 517 (M+1). R_t = 6.50 min.**EXAMPLE 512 (general procedure (V))**10 **4-[[[(4-*tert*-Butylcyclohexyl)-(4-benzylbenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**¹H NMR (DMSO): δ 8.07 (d, 2H); 7.60-7.15 (m, 11H)15 HPLC-MS (Method D): m/z = 551 (M+1). R_t = 6.23 min.**EXAMPLE 513 (general procedure (V))****4-[[[(4-*tert*-Butylcyclohexyl)-(4-isopropoxybenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide**

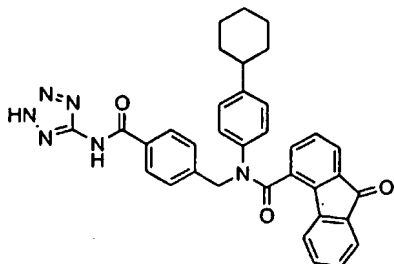
20

¹H NMR (DMSO): δ 8.10 (d, 2H); 7.60-7.40 (m, 4H); 4.80-4.70 (m, 3H).HPLC-MS (Method D): m/z = 519 (M+1). R_t = 5.87 min.

HPLC-MS (Method D): m/z = 571 ($M+1$). R_t = 6.27 min.

EXAMPLE 509 (general procedure (V))

- 5 4-[[[(4-Cyclohexylphenyl)-(9-oxo-9H-fluorene-4-carbonyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

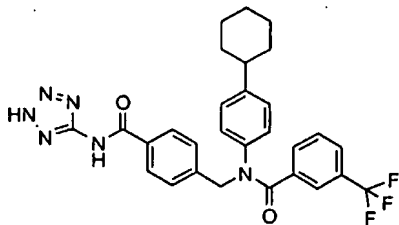


- 10 ^1H NMR (DMSO): δ 8.17 (d, 2H); 7.72 (d, 1H); 7.68-7.62 (m, 3H); 7.55-7.50 (m, 2H); 7.45 (d, 1H); 7.25 (t, 1H); 7.05 (d, 2H); 7.02 (d, 2H); 5.30 (s, 2H).

HPLC-MS (Method D): m/z = 583 ($M+1$). R_t = 5.63 min.

EXAMPLE 510 (general procedure (V))

- 15 4-[[[(4-Cyclohexylphenyl)-(3-trifluoromethylbenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

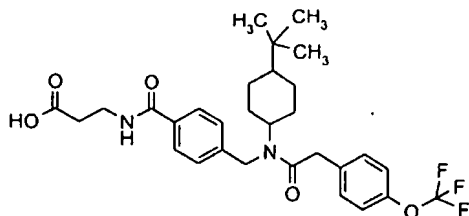


- 20 ^1H NMR (DMSO): δ 8.09 (d, 2H); 7.76 (d, 1H); 7.71 (d, 1H); 7.59-7.55 (m, 4H); 7.12 (s, 4H); 5.30 (s, 2H).

HPLC-MS (Method D): m/z = 549 ($M+1$). R_t = 5.87 min.

EXAMPLE 506 (general procedure (V))

3-[4-((4-*tert*-Butylcyclohexyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl]benzoyl-amino]propionic acid



5

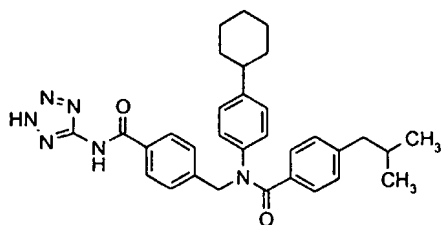
^1H NMR (DMSO. Isomers): δ 8.57 + 8.51 (t, 1H); 7.90 + 7.79 (d, 2H); 7.50-7.30 (m, 6H); 4.74 + 4.60 (s, 2H).

HPLC-MS (Method D): m/z = 563 ($M+1$). R_t = 5.73 min.

10

EXAMPLE 507 (general procedure (V))

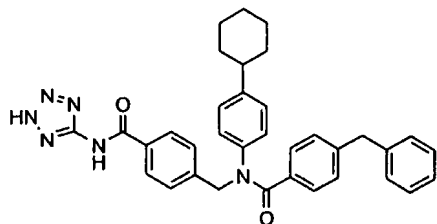
4-[[[4-(4-Cyclohexylphenyl)-(4-isobutylbenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



15 HPLC-MS (Method D): m/z = 537 ($M+1$). R_t = 6.57 min.

EXAMPLE 508 (general procedure (V))

4-[[[4-(4-Cyclohexylphenyl)-(4-benzylbenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

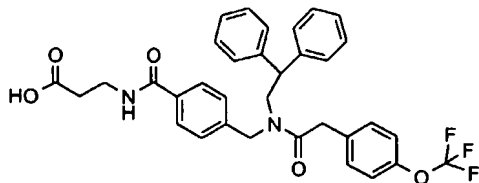


20

^1H NMR (DMSO): δ 8.09 (d, 2H); 7.55 (d, 2H); 7.34-7.30 (m, 4H); 7.26-7.04 (m, 9H); 5.20 (s, 2H).

EXAMPLE 504 (general procedure (V))

3-[4-({(2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl}benzoylamino)-propionic acid



5

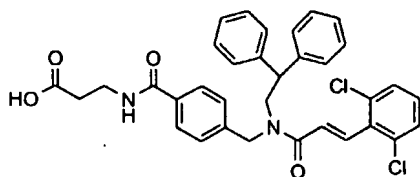
¹H NMR (DMSO): δ 8.58 (t, 1H); 8.53 (t, 1H); 7.88 (d, 2H); 7.82 (d, 2H); 7.47-7.26 (m, 28 H); 7.20 (d, 2H); 7.15 (d, 2H); 4.62 (s, 2H); 4.52 (t, 2H); 4.41 (s, 2H); 4.08 (d, 2H); 4.03 (d, 2H).

HPLC-MS (Method D): m/z = 605 (M+1). R_t = 5.33 min.

10

EXAMPLE 505 (general procedure (V))

3-(4-({[3-(2,6-Dichlorophenyl)acryloyl]-(2,2-diphenylethyl)amino)methyl}benzoylamino)-propionic acid



15

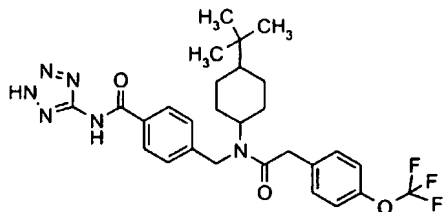
¹H NMR (DMSO): δ 8.55 (t, 1H); 7.84 (dd, 2H); 7.83-7.24 (m, 16); 7.18+6.95 (d, 1H); 4.70-4.50 (m, 3H); 4.21 (t, 2H).

HPLC-MS (Method D): m/z = 601 (M+1). R_t = 5.33 min.

20

EXAMPLE 502 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



5

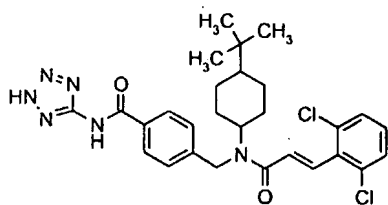
¹H NMR (DMSO. Isomers 2:1): δ 8.17 + 8.07 (d, 2H); 7.55-7.45 (m, 2H); 7.45-7.30 (m, 4H); 4.80 + 4.64 (s, 2H).

HPLC-MS (Method D): m/z = 559 (M+1). R_t = 5.97 min.

10

EXAMPLE 503 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



15

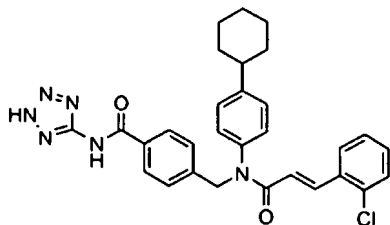
¹H NMR (DMSO. Isomers 1:1): δ 8.18-8.12 (m, 2H); 7.68-7.30 (m, 7H); 6.85 (d, 1H); 4.88 (s, 1H); 4.79 (s, 1H).

HPLC-MS (Method D): m/z = 555 (M+1). R_t = 6.13 min.

20

EXAMPLE 500 (general procedure (V))

4-([3-(2-Chlorophenyl)acryloyl]-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

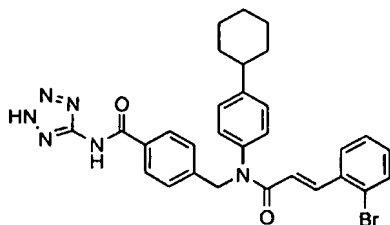
¹H NMR (DMSO): δ 8.11 (d, 2H); 7.94 (d, 1H); 7.59 (d, 1H); 7.51 (d, 2H); 7.53 (t, 2H); 7.40 (d, 1H); 7.36 (d, 2H); 7.28 (d, 2H); 6.55 (d, 1H); 5.19 (s, 2H).

HPLC-MS (Method D): m/z = 541 (M+1). R_t = 6.13 min.

10

EXAMPLE 501 (general procedure (V))

4-([3-(2-Bromophenyl)acryloyl]-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



15

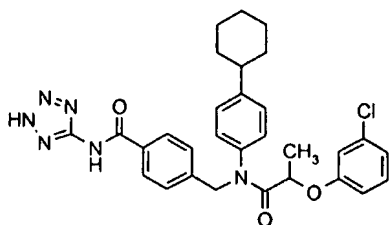
¹H NMR (DMSO): δ 8.11 (d, 2H); 7.91 (d, 1H); 7.76 (d, 1H); 7.52 (d, 2H); 7.43-7.30 (m, 5H); 7.28 (d, 2H); 6.50 (d br, 1H); 5.19 (s, 2H);

HPLC-MS (Method D): m/z = 587 (M+1). R_t = 6.23 min.

20

EXAMPLE 498 (general procedure (V))

4-[[[2-(3-Chlorophenoxy)propionyl]-(4-cyclohexylphenyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

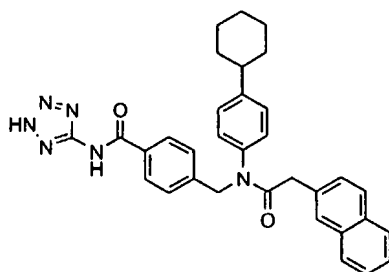
^1H NMR (DMSO): δ 8.09 (d, 2H); 7.41 (d, 2H); 7.33 (t, 1H); 7.29 (d, 2H); 7.23 (d, 2H); 7.08 (d, 1H); 6.75, (m, 2H); 5.10 (d, 1H); 4.92 (d, 1H); 4.82 (q, 1H).

HPLC-MS (Method D): m/z = 559 ($M+1$). R_t = 6.10 min.

10

EXAMPLE 499 (general procedure (V))

4-[[[2-(4-Cyclohexylphenyl)-2-naphthylacetyl]amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



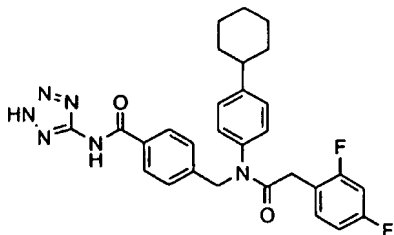
15

^1H NMR (DMSO): δ 8.09 (d, 2H); 9.95 (m, 1H); 7.92-7.85 (m, 2H); 7.58-7.54 (m, 3H); 7.48 (d, 2H); 7.32 (d, 3H); 7.24 (d, 2H); 5.05 (s, 2H).

HPLC-MS (Method D): m/z = 545 ($M+1$). R_t = 6.23 min.

EXAMPLE 496 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[2-(2,4-difluorophenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

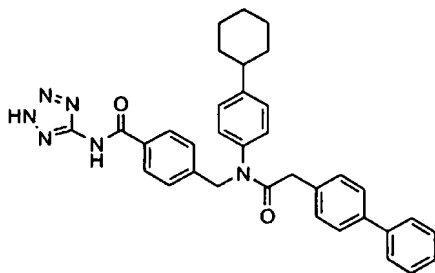
^1H NMR (DMSO): δ 8.11 (d, 2H); 7.48 (d, 2H); 7.38-7.32 (m, 3H); 7.27-7.20 (m, 3H); 7.08 (t, 1H); 5.03 (s, 2H).

HPLC-MS (Method D): m/z = 531 ($M+1$). R_t = 5.87 min.

10

EXAMPLE 497 (general procedure (V))

4-(((2-Biphenyl-4-yl-acetyl)-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



15

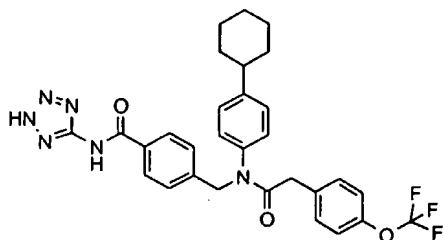
^1H NMR (DMSO): δ 8.10 (d, 2H); 7.72 (d, 2H); 7.64 (d, 2H); 7.54 (t, 2H); 7.48 (d, 2H); 7.43 (t, 1H); 7.34 (d, 2H); 7.26-7.21 (m, 4H); 5.02 (s, 2H).

HPLC-MS (Method D): m/z = 571 ($M+1$). R_t = 6.50 min.

20

EXAMPLE 494 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



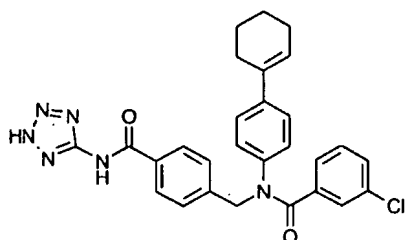
5

^1H NMR (DMSO): δ 8.09 (d, 2H); 7.47 (d, 2H); 7.33-7.22 (m, 8H); 5.03 (s, 2H).

HPLC-MS (Method D): m/z = 579 (M+1). R_t = 6.27 min.

10 **EXAMPLE 495**

4-(((4-Cyclohex-1-enylphenyl)-(3-chlorobenzoyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



15 ^1H NMR (DMSO): δ 12.4 (s, 1H), 8.02 (d, 2H), 7.50 (d, 2H), 7.35 (m, 1H), 7.42 (s, 1H), 7.25 (m, 4H), 7.06 (d, 2H), 6.12 (t, 1H), 5.19 (s, 2H), 2.22 (m, 2H), 2.12 (m, 2H), 1.65 (m, 2H), 1.55 (m, 2H)

390

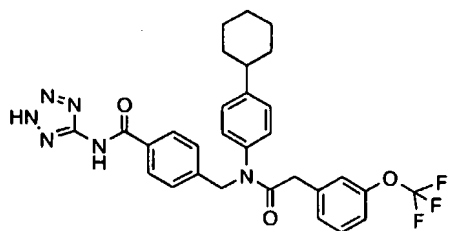
¹H NMR (DMSO): δ 8.09 (d, 2H); 7.41 (d, 2H); 7.34 (d, 2H); 7.25 (dd, 4H); 6.75 (d, 2H); 5.00 (d, 2H); 4.61 (d, 1H).

HPLC-MS (Method D): m/z = 559 (M+1). R_t = 6.10 min.

5

EXAMPLE 492 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



10

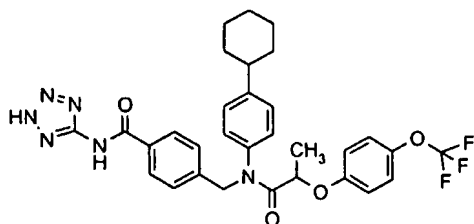
¹H NMR (DMSO): δ 8.10 (d, 2H); 7.45 (m, 3H); 7.30 (m, 3H); 7.20 (m, 3H); 7.08 (s, 1H); 5.03 (s, 1H).

HPLC-MS (Method D): m/z = 579 (M+1). R_t = 6.23 min.

15

EXAMPLE 493 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[2-(4-trifluoromethoxyphenoxy)propionyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



20

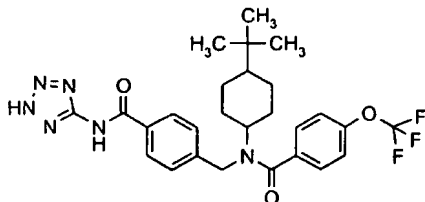
¹H NMR (DMSO): δ 8.10 (d, 2H); 7.43 (d, 2H); 7.31 (d, 2H); 7.25 (s, 4H); 6.83 (d, 2H); 5.01 (dd, 2H); 4.83 (q, 1H).

HPLC-MS (Method D): m/z = 609 (M+1). R_t = 6.27 min.

25

EXAMPLE 489 (general procedure (V))

4-[[[(4-*tert*-Butylcyclohexyl)-(4-trifluoromethoxybenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



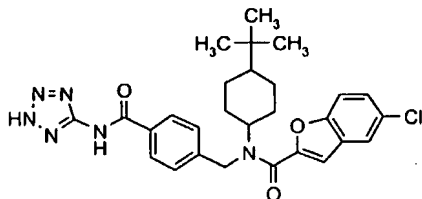
5

^1H NMR (DMSO): δ 8.14 (d, 2H); 7.70-7.40 (m, 6H); 4.82 (s, 2H).

HPLC-MS (Method D): m/z = 545 ($M+1$). R_t = 5.70 min.

10 EXAMPLE 490 (general procedure (V))

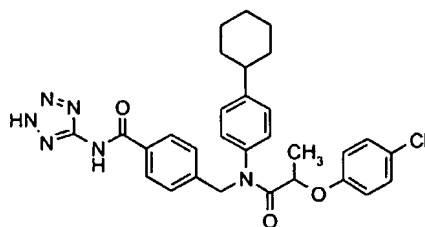
5-Chlorobenzofuran-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbonyl)-benzyl]amide

15 ^1H NMR (DMSO): δ 8.13 (d, 2H); 7.90 (s, 1H); 7.54 (dd, 4H); 4.98 (s, 1H).

HPLC-MS (Method D): m/z = 535 ($M+1$). R_t = 6.10 min.

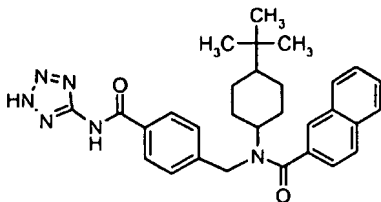
EXAMPLE 491 (general procedure (V))

20 4-[[[2-(4-Chlorophenoxy)propionyl]-[4-(cyclohexylphenyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



EXAMPLE 486 (general procedure (V))

Naphtalene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-
amide



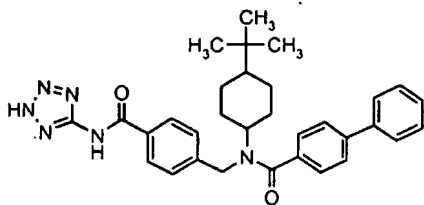
5

HPLC-MS (Method E): m/z = 511 ($M+1$). R_t = 3.47 min.

EXAMPLE 487 (general procedure (V))

Biphenyl-4-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-
amide

10

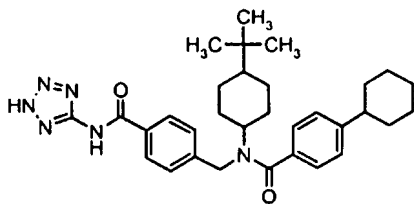


^1H NMR (DMSO): δ 8.15 (d, 2H); 7.90-7.40 (m, 9H); 4.84 (s, 2H).

15 HPLC-MS (Method D): m/z = 537 ($M+1$). R_t = 6.13 min.

EXAMPLE 488 (general procedure (V))

4-[[4-(4-*tert*-Butylcyclohexyl)-(4-cyclohexylbenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-
benzamide



20

^1H NMR (DMSO): δ 8.13 (d, 2H); 7.70-7.30 (m, 6H); 4.79 (s, 1H).

387

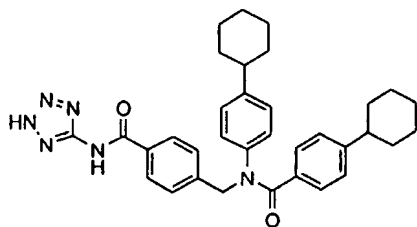
^1H NMR (DMSO): δ 8.09 (d, 2H); 8.09 (d, 4H); 7.84 (d, 2H); 7.65 (d, 2H); 7.57 (m, 3-4H); 7.12 (s, 4H); 5.24 (s, 2H).

HPLC-MS (Method E): m/z = 559 (M+1). R_t = 2.77 min.

5

EXAMPLE 484 (general procedure (V))

4-[[[(4-Cyclohexylphenyl)-(4-cyclohexylbenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

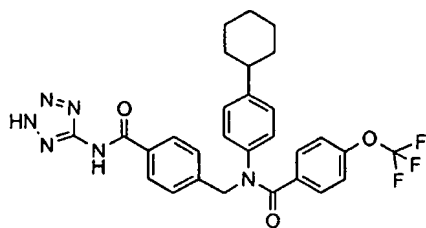


10 ^1H NMR (DMSO): δ 8.08 (d, 2H) 7.53 (d, 2H); 7.30 (d, 2H); 7.15-7.05 (m, 6H); 5.21 (s, 2H).

HPLC-MS (Method E): m/z = 563 (M+1). R_t = 3.99 min.

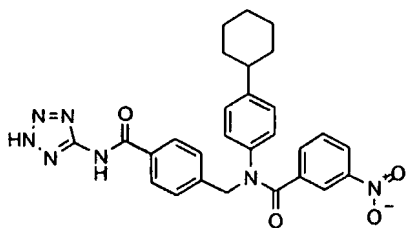
EXAMPLE 485 (general procedure (V))

15 4-[[[(4-Cyclohexylphenyl)-(4-trifluoromethoxybenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide



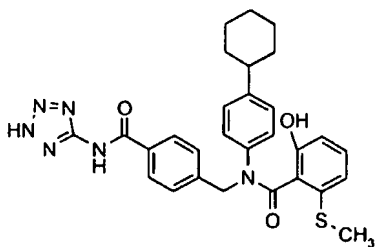
20 ^1H NMR (DMSO): δ 8.09 (d, 2H); 7.56 (d, 2H); 7.51 (d, 2H); 7.28 (d, 2H); 7.10 (dd, 4H); 5.24 (s, 2H).

HPLC-MS (Method E): m/z = 565(M+1). R_t = 3.52 min.

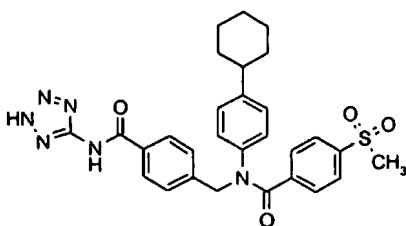
EXAMPLE 481 (general procedure (V))4-[[[(4-Cyclohexylphenyl)-(3-nitrobenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

- 5 ^1H NMR (DMSO): δ 8.20 (d, 1H); 8.17 (s, 1H); 8.09 (d, 2H); 7.81 (d, 1H); 7.60 (m, 3H); 7.14 (dd, 4H); 5.29 (s, 2H).

HPLC-MS (Method E): m/z = 526 ($M+1$). R_t = 3.18 min.

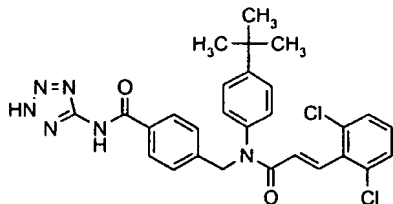
10 EXAMPLE 482 (general procedure (V))4-[[[(4-Cyclohexylphenyl)-(2-hydroxy-6-methylsulfanylbzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

- 15 HPLC-MS (Method E): m/z = 543 ($M+1$). R_t = 3.25 min.

EXAMPLE 483 (general procedure (V))4-[[[(4-Cyclohexylphenyl)-(4-methylsulfonylbzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

EXAMPLE 479 (general procedure (V))

4-(((4-*tert*-butylphenyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

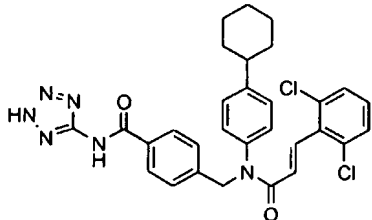
^1H NMR (DMSO): δ 8.10 (d, 2H); 7.68 (d, 1H); 7.56-7.48 (m, 6H); 7.41 (t, 1H); 7.26 (d, 2H); 6.56 (d, 1H); 5.17 (s, 2H).

HPLC-MS (Method E): m/z = 549 (M+1). R_t = 3.47 min.

10

EXAMPLE 480 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

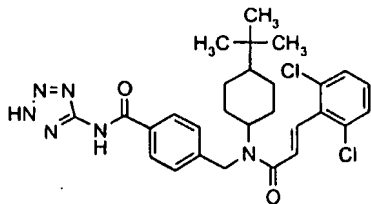
^1H NMR (DMSO): δ 8.07 (d, 2H); 7.67 (d, 1H); 7.55 (d, 2H); 7.49 (d, 2H); 7.40 (t, 1H); 7.32 (d, 2H); 7.23 (d, 2H); 6.55 (d, 1H); 5.16 (d, 2H).

HPLC-MS (Method E): m/z = 575 (M+1). R_t = 3.76 min.

20

EXAMPLE 477 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



5

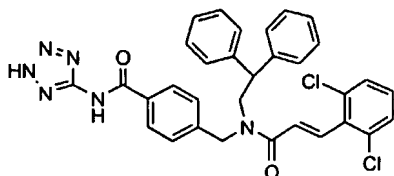
¹H NMR (DMSO. Isomers ca 1:1): δ 8.20 (m, 2H); 7.60 (m, 6H); 6.84 (d, 1H); 4.88(s, 1H); 4.78 (s, 1H).

HPLC-MS (Method E): m/z = 555 (M+1). R_t = 3.39, 3.45 min.

10

EXAMPLE 478 (general procedure (V))

4-([3-(2,6-Dichlorophenyl)acryloyl]-(2,2-diphenylethyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

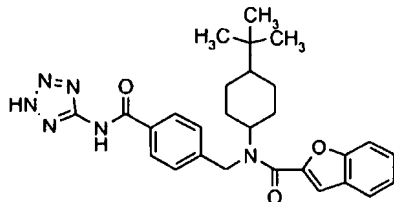
¹H NMR (DMSO. Isomers ca 1:1): δ 8.11 (s, 2H); 7.70-7.25 (m, 16 H); 7.20 (d, 1H); 6.93 (d, 1H); 4.63 (s, 1H); 4.57 (s, 1H); 4.50 (t, 1H); 4.26 (d, 2H).

HPLC-MS (Method E): m/z = 598 (M+1). R_t = 3.09 min.

20

EXAMPLE 475 (general procedure (V))

Benzofuran-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-amide



5

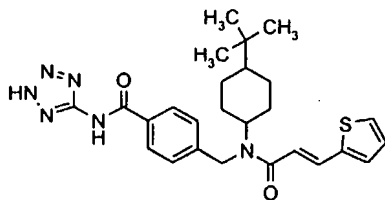
¹H NMR (DMSO. Isomers ca 1:1): δ 8.13 (d, 2H); 7.95-7.65 (m, 2H); 7.56 (d, 2H); 7.55-7.30 (m, 2H); 4.88 (s br, 2H); 4.23 (s br, 1H).

HPLC-MS (Method E): m/z = 501 (M+1). R_t = 3.20 min.

10

EXAMPLE 476 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-(3-thiophen-2-ylacryloyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

¹H NMR (DMSO. Isomers ca 1:1): δ 8.20-8.05 (m, 2H); 7.80-7.40 (m, 4H); 7.40-6.85 (2H); 4.87 (s, 1H); 4.75 (s, 1H).

HPLC-MS (Method E): m/z = 495 (M+1). R_t = 3.07 min.

20

Step D: Resin bound benzo[b]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]amide

To the above resin bound 4-[(4-*tert*-butylcyclohexylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide was added a solution of benzo[b]thiophene-2-carboxylic acid (400 μ mol) in a mixture of NMP, DCP and diisopropylethylamine (4.5:4.5:1, 1 mL) followed by a solution of Py-BrOP (400 μ mol) in DCP (500 μ L). The mixture was allowed to react 3 hours at 50 °C. The resin was cooled to 25 °C while washed with NMP (4 x 1 mL), and DCM (10 x 1 mL).

Step E: Benzo[b]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]amide

The above resin bound benzo[b]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]amide (50 mg) was treated with 1.2 mL 20% trifluoroacetic acid in dichloromethane for 1 hour at 25°C. The product was filtered off and concentrated in vacuo to afford the title compound.

¹H NMR (DMSO): δ 8.14 (d, 2H); 8.1-7.9 (m, 2H); 7.81 (s, 2H); 7.60-7.50 (m, 3H); 4.96 (s, 1H); 4.89 (s br, 1H).

HPLC-MS (Method D): m/z = 517 (M+1). R_t = 5.80 min.

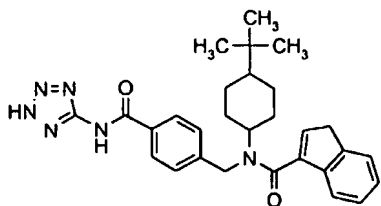
20

The following examples can be made as described above.

EXAMPLE 474 (general procedure (V))

3*H*-Indene-1-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-amide

25



¹H NMR (DMSO): δ 8.15 (d, 2H); 7.70-7.30 (m, 6H); 6.82 (d, 1H)

30 HPLC-MS (Method E): m/z = 499 (M+1). R_t = 3.07 min.

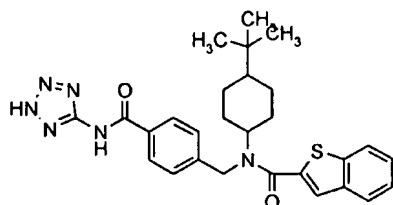
dichloroethane, 1,2-dichloropropane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. The reaction is performed between 20°C and 60°C, preferably at 50°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

Step E:

Step E is identical to step E of general procedure (S).

10 EXAMPLE 473 (general procedure (V))

Benzo[*b*]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]amide



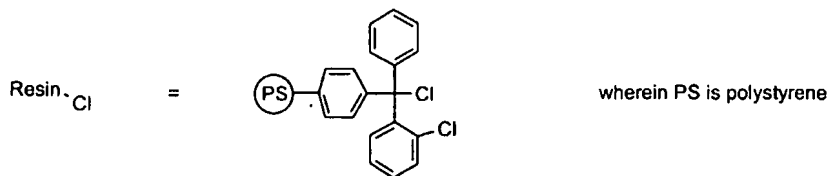
15 Step A: Resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide

150 μmol 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide was dissolved in a mixture of 250 μL dichloromethane, 250 μL DMF and 100 μL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with 2-chlorotriyl chloride. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step C: Resin bound 4-[(4-*tert*-butylcyclohexylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

The above resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide (50 mg) was treated with a 0.5 M solution of 4-*tert*-butylcyclohexylamine (0.25 mmol, 38.75 mg) in a mixture of NMP and trimethylorthoformate (1:1, 0.5 mL) and glacial acetic acid (50 μL) for 1 hour at 25°C followed by sodium cyanoborohydride (250 μmol, 16 mg) dissolved in a mixture of NMP and methanol (1:1, 0.25 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of NMP and methanol (1:1, 2 x 1 mL), NMP (3 x 1 mL) and a mixture of 1,2-dichloropropane (DCP) and diisopropylethylamine (7:1, 2 x 1 mL) afforded the desired product.

wherein r is as defined for formula (I), and



5 Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of a nucleophilic Fmoc protected amine (V-A-Fmoc) or (IV) in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine.

- 10 Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotritylchloride.

15

Step B:

Step B is identical to step B of general procedure (S).

Step C:

- 20 Step C is identical to step C of general procedure (S).

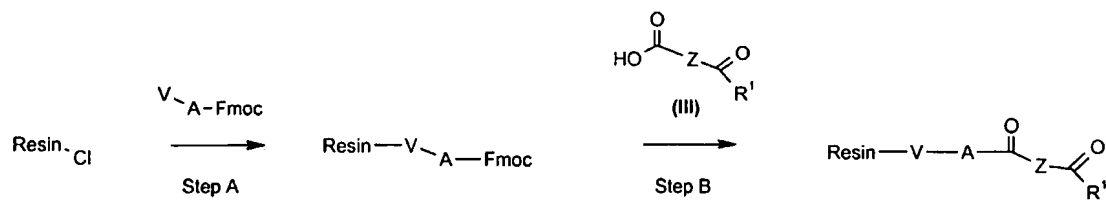
Step D:

The acylation (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) is performed by adding an excess of D-X-OH in a solvent such as DMF, *N*-methylpyrrolidinone,

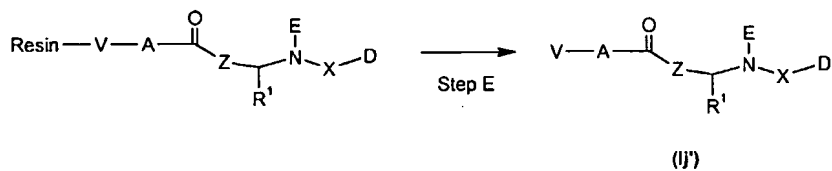
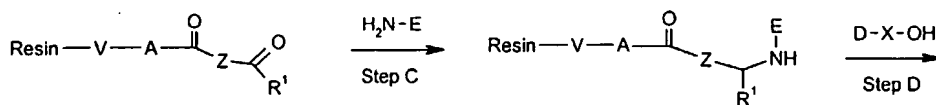
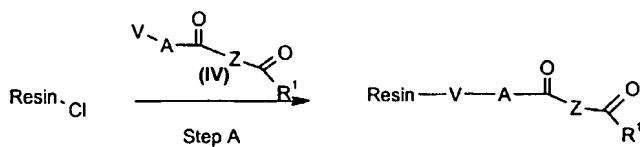
- 25 THF, dichloromethane, 1,2-dichloroethane, 1,2-dichloropropane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (PyBrOP) or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-
- 30

General procedure (V) for the solid phase synthesis of compounds of the general formula (II'):

Alternatively, the solid support used in general procedure (B) can be a 2-chlorotrityl polystyrene resin.



OR



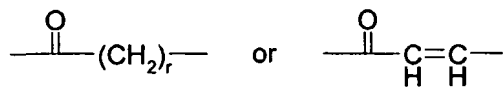
5

wherein

V, A, Z, R¹, E and D are as defined for formula (I),

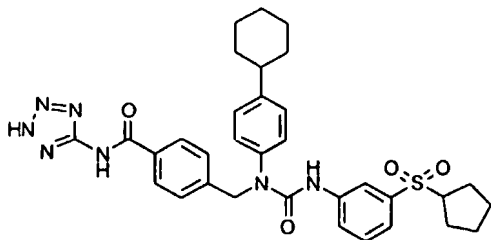
10

X is



EXAMPLE 471 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopentylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



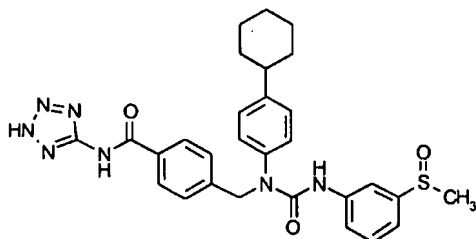
5

HPLC-MS (method B): m/z: 628, R_t = 7.55 min.

EXAMPLE 472 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfinylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

10



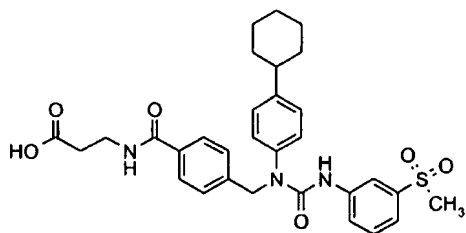
^1H NMR ($\text{DMSO}-d_6$): δ 8.58(s, 1H), 7.99(d, 2H), 7.80(s, 1H), 7.63(d, 1H), 7.42(d, 2H), 7.40(d, 1H), 7.20(dd, 4H), 5.00(s, 2H), 2.70(s, 3H), 1.85-1.15 (m, 10H).

15

HPLC-MS (method B): m/z: 558, R_t = 6.22 min.

EXAMPLE 469 (general procedure (U))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]benzoylamino}-propionic acid



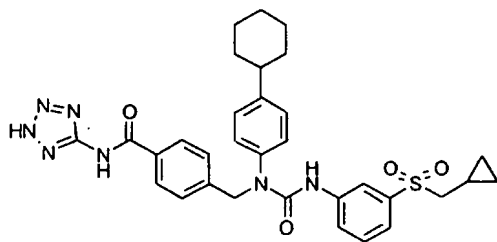
5

^1H NMR ($\text{DMSO}-d_6$): δ 8.65 (s, 1H); 8.51 (t, 1H); 8.05 (s, 1H); 8.78 (m, 1H); 7.75 (d, 2H); 7.45 (m, 2H); 7.30 (d, 2H); 7.22 (d, 2H); 7.12 (d, 2H); 4.95 (s, 2H); 3.40 (m); 3.15 (s, 3H); 2.43 (t, 2H); 1.90-1.15 (m)

10 HPLC-MS (Method B): m/z = 578 ($M+1$). R_t = 6.32 min.

EXAMPLE 470 (general procedure (U))

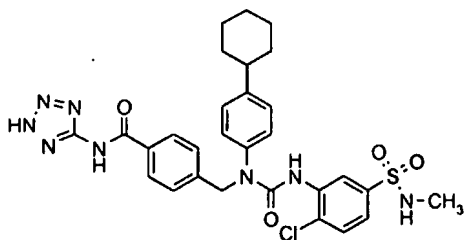
4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopropylmethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

HPLC-MS (method B): m/z : 614, R_t = 7.35 min.

376

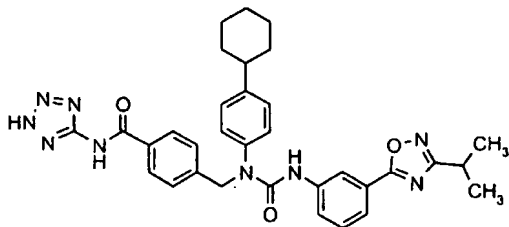
EXAMPLE 467 (general procedure (U))4-[3-(2-Chloro-5-methylsulfamoylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

5

¹H NMR (DMSO-*d*₆): δ 8.5 (d, 1H); 7.76 (d br, 2H); 7.60-7.35 (m, 5H); 7.32 (s, 4H); 5.00 (s, 2H); 2.43 (d, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H)

HPLC-MS (Method B): *m/z* = 623 (*M*+1). *R*_t = 7.82 min.

10

EXAMPLE 468 (general procedure (U))4-{1-(4-Cyclohexylphenyl)-3-[3-(3-isopropyl-[1,2,4]oxadiazol-5-yl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide

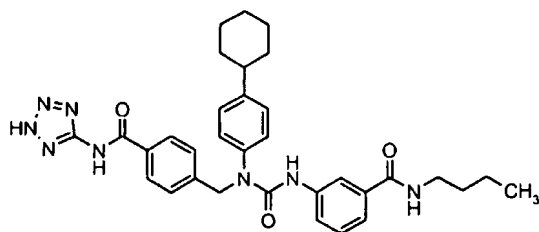
15

The oxadiazole was prepared by using *N*-hydroxy-isobutyramidine as nucleophile instead of an amine as described in example 458. After cleavage from the resin, ring closure to the oxadiazole was conducted in refluxing toluene.

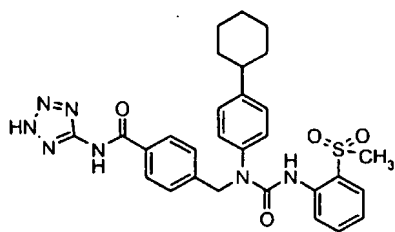
¹H NMR (DMSO-*d*₆): δ 12.05 (s br, 1H); 8.68 (s, 1H); 8.28 (s, 1H); 8.05 (d, 2H); 7.80 (d, 1H); 7.63 (d, 1H); 7.55-7.45 (m, 3H); 7.20 (s, 4H); 5.04 (s, 2H); 3.12 (h, 1H); 1.85-1.65 (m, 5H); 1.50-1.15 (m+d, 11H)

HPLC-MS (Method B): *m/z* = 624 (*M*+1). *R*_t = 8.07 min.

25

EXAMPLE 465 (general procedure (U))N-Butyl-3-{3-(4-cyclohexylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)-benzyl]ureido}benzamide

- 5 ^1H NMR (300 MHz, DMSO- d_6): δ 11.35 (s br, 1H); 8.55 (m, 2H); 8.05 (d, 2H); 7.70 (s, 1H); 7.62 (d, 1H); 7.42 (m, 3H); 7.35-7.10 (m, 5H); 5.00 (s, 2H); 1.85-1.10 (m, 15H); 0.90 (t, 3H).

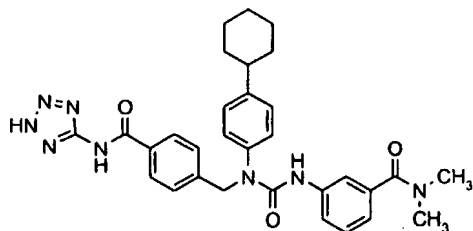
HPLC-MS (method B): m/z = 595, R_t = 7.48 min.10 EXAMPLE 466 (general procedure (U))4-[1-(4-Cyclohexylphenyl)-3-(2-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

- 15 ^1H NMR (DMSO- d_6): δ 12.40 (s, 1H); 8.50-8.45 (s+d, 2H); 8.05 (d, 2H); 7.68 (d, 1H); 7.65 (t, 1H); 7.52 (d, 2H); 7.22 (s, 4H); 7.18 (t, 1H); 5.00 (s, 2H); 3.00 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H)

HPLC-MS (Method B): m/z = 574 ($M+1$). R_t = 7.38 min

EXAMPLE 463 (general procedure (U))

N,N-Dimethyl-3-{3-(4-cyclohexylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]ureido}benzamide



5

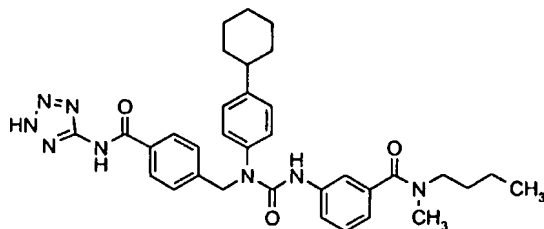
¹H NMR (300 MHz, DMSO-*d*₆): δ 12.30 (s br, 1H); 8.35 (s, 1H); 8.05 (d, 2H); 7.50 (m, 4H); 7.20 (m, 5H); 6.95 (d, 1H); 5.00 (s, 2H); 3.15 (s, 3H); 2.94 (d br, 6H); 1.85-1.15 (m, 11H).

HPLC-MS (method B): *m/z* = 567, *R*_t = 6.47 min.

10

EXAMPLE 464 (general procedure (U))

N-Butyl-*N*-methyl-3-{3-(4-cyclohexylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]ureido}-benzamide



15

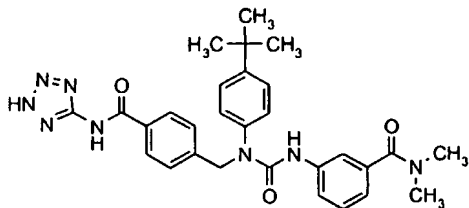
¹H NMR (300 MHz, DMSO-*d*₆): δ 12.30 (s br, 1H); 8.35 (s, 1H); 8.05 (d, 2H); 7.48 (m, 4H); 7.35-7.20 (m, 5H); 6.95 (d, 1H); 5.00 (s, 2H); 2.92 (d br, 3H); 1.85-0.70 (m, 18H).

HPLC-MS (method B): *m/z* = 609, *R*_t = 7.51 min.

20

EXAMPLE 461 (general procedure (U))

N,N-Dimethyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}-benzamide



5

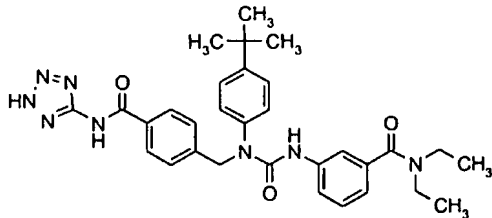
^1H NMR (200 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.40 (s, 1H); 8.05 (d, 2H); 7.55-7.15 (m, 9H); 6.98 (d, 1H); 5.03 (s, 2H); 2.95 (d, br, 6H); 1.30 (s, 9H).

HPLC-MS (method B): m/z = 541, R_t = 5.80 min.

10

Example 462 (general procedure (U))

N,N-Diethyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}-benzamide



15

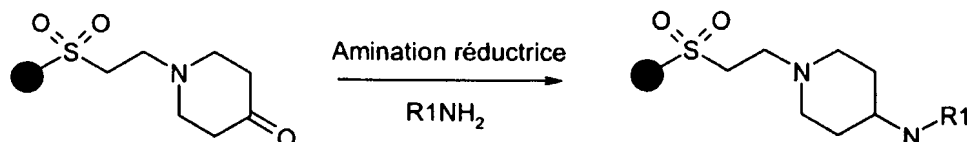
^1H NMR (200 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.40 (s, 1H); 8.05 (d, 2H); 7.50-7.18 (m, 9H); 6.95 (d, 1H); 5.01 (s, 2H); 3.24 (s, br, 4H); 1.30 (s, 9H); 1.10 (s, br, 6H).

HPLC-MS (method B) m/z = 569, R_t = 6.77 min.

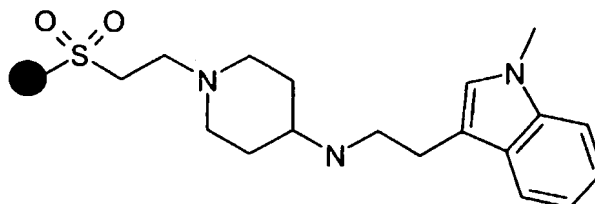
20

D2) Amination réductrice sur support solide

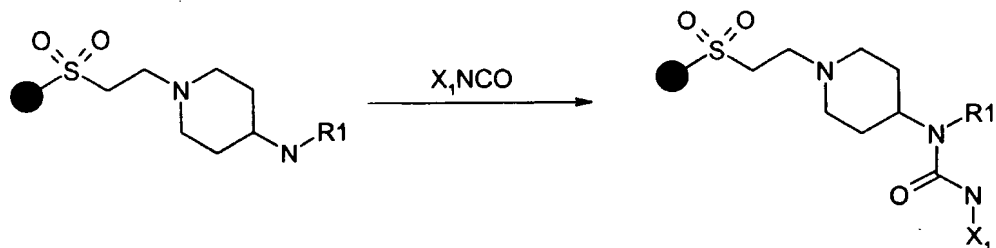
Elle s'effectue selon la procédure décrite dans la littérature (Pelter, A. ; Rosser, R.M. *J. Chem. Soc. Perkin Trans I* 1984, 717-720 ; Bomann, M.D.; Guch, I.C. ; DiMare, M. *J. Org. Chem.* 1995, 60, 5995-5996 ; Khan, N.M. ; Arumugam, V. ;
5 Balasubramanian, S. *Tetrahedron Lett.* 1996, 37, 4819-4822) suivant le schéma :



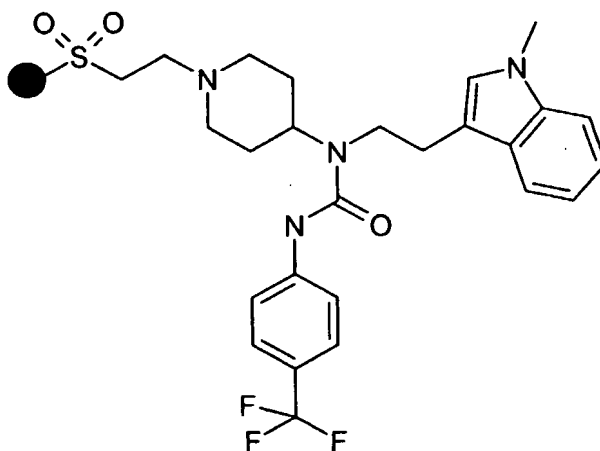
Procédure générale : à la résine cétonique prégonflée dans le triméthylorthoformiate (TMOF) est ajoutée l'amine primaire (5 à 10 éq.) puis le mélange est soniqué. On ajoute ensuite le complexe de borane pyridine (8 M, 5 à 10 éq.) et le mélange est
10 agité 12 à 72 heures. La résine est filtrée, lavée avec des solvants tels que le dichlorométhane, la diméthylformamide, le méthanol et le tétrahydrofurane puis séchée sous vide.

Préparation 5

15 1 g (taux de charge de 1 mmol/g, 1 mmol) de résine cétonique sont prégonflés dans le TMOF. On ajoute ensuite la 2-(1-méthyl-1H-indol-3-yl)éthylamine (1,01 g, 10 mmol, 10 éq.) puis le complexe de borane pyridine (8M, 1,25 ml, 10 mmol, 10 éq.). Le mélange est agité 48 heures à température ambiante. La résine est filtrée, rincée successivement avec du dichlorométhane, du diméthylformamide, du
20 méthanol, du tétrahydrofurane et du dichlorométhane puis séchée sous vide. 1,05 g de résine jaune pâle sont ainsi obtenus avec un taux de charge de 0,91 mmol/g calculé d'après l'analyse élémentaire de l'azote.

D3) Fonctionnalisation de l'amine secondaire**D3a) Fonctionnalisation avec des isocyanates**

Procédure générale : la résine "amine secondaire" est prégonflée dans un solvant tel que le dichlorométhane ou la diméthylformamide avant l'addition de l'isocyanate (3 à 10 éq.). Le mélange est agité 1 à 24 heures à température ambiante. La résine est alors filtrée, lavée avec des solvants tels que le dichlorométhane, la diméthylformamide et le tétrahydrofurane puis séchée sous vide.

Préparation 6

55 mg (50 μ mol) de la résine (voir préparation 5) sont prégonflés dans du dichlorométhane anhydre. On ajoute ensuite le 4-trifluorophénylisocyanate (28 mg, 150 μ mol, 3 éq.) et le tout est agité 2 heures à température ambiante. La résine est filtrée, rincée au tétrahydrofurane, au diméthylformamide, au tétrahydrofurane puis au dichlorométhane avant d'être séchée sous vide.

D3b) Fonctionnalisation avec des chlorures de sulfonyles

Le mode opératoire de fonctionnalisation est identique à celui exposé au point B3b.

D3c) Fonctionnalisation avec des chlorures d'acides

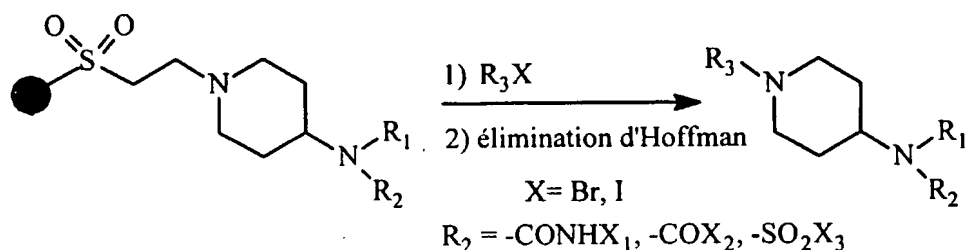
Le mode opératoire de fonctionnalisation est identique à celui exposé au point B3c.

D3d) Fonctionnalisation avec des acides carboxyliques

Le mode opératoire de fonctionnalisation est identique à celui exposé au point B3d.

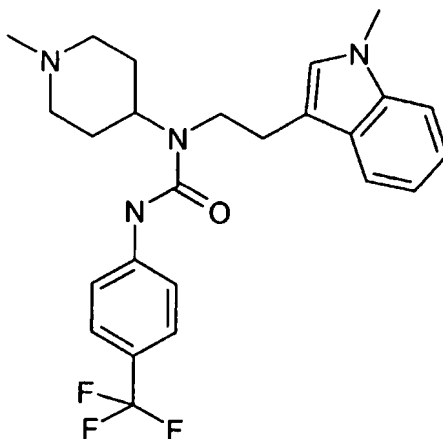
D4) Etape de clivage

- 5 L'étape de clivage décrite ci-dessous est valable quelle que soit la fonctionnalisation opérée au préalable sur l'amine secondaire :



- Procédure générale : la résine disubstituée est gonflée dans des solvants tels que le dichlorométhane, la diméthylformamide ou le tétrahydrofurane puis est ajouté
- 10 l'halogénure R_3X dans lequel R_3 a la signification indiquée précédemment et X représente un atome d'halogène (5 éq.) et le mélange agité toute la nuit à une température comprise entre 20 et 60° C. La résine est filtrée, rincée avec des solvants tels que la diméthylformamide, le tétrahydrofurane, le méthanol et le dichlorométhane puis séchée sous vide. La résine est regonflée dans le
- 15 dichlorométhane et de la résine échangeuse d'ions basiques (Ouyang, X. ; Armstrong, R.W. ; Murphy, M.M. *J. Org. Chem.* **1998**, *63*, 1027-1032) est ajoutée. Le tout est agité 48 heures à température ambiante. Les résines sont filtrées, rincées au dichlorométhane et le filtrat concentré sous vide.

Exemple D4 : Urée de *N*-[2-(1-méthyl-1*H*-indol-3-yl)éthyl]-*N*-(1-méthyl-4-pipéridinyl)-*N'*-[4-(trifluorométhyl)phényle] ($C_{25}H_{29}F_3N_4O$, $M = 458,5$)

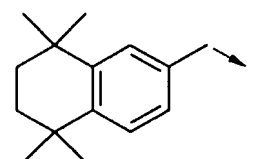
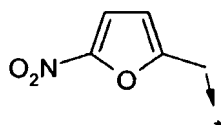
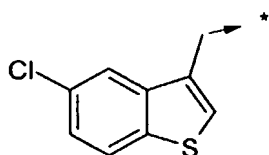
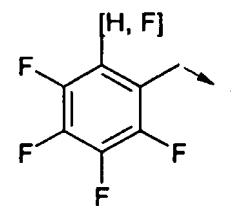
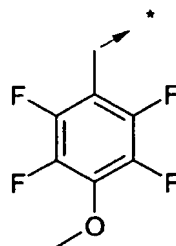
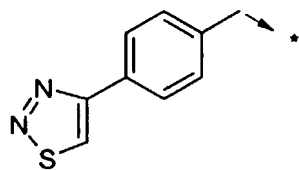
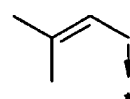
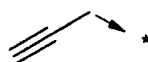
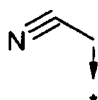
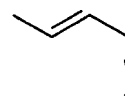
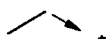
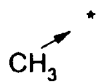


5 55 mg (50 μ mol) de la résine urée sont gonflés dans de la diméthylformamide puis 35 mg (250 μ mol, 5 éq.) de iodométhane sont ajoutés et le mélange agité 18 heures à température ambiante. La résine est filtrée, rincée avec de la diméthylformamide, du tétrahydrofurane, du méthanol et du dichlorométhane puis séchée sous vide. La résine est regonflée dans du dichlorométhane puis environ 100 mg de résine
10 amberlite IRA68 sont ajoutés et le mélange agité 48 heures. Les résines sont filtrées, rincées avec du dichlorométhane et le filtrat concentré pour donner 18 mg (rdt = 78 %) d'une huile incolore.

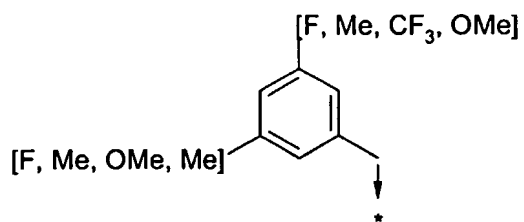
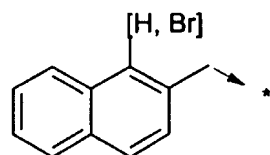
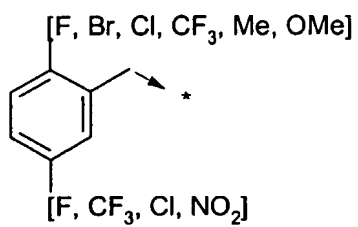
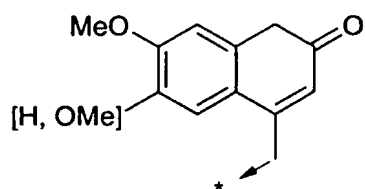
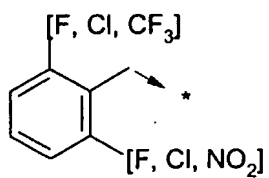
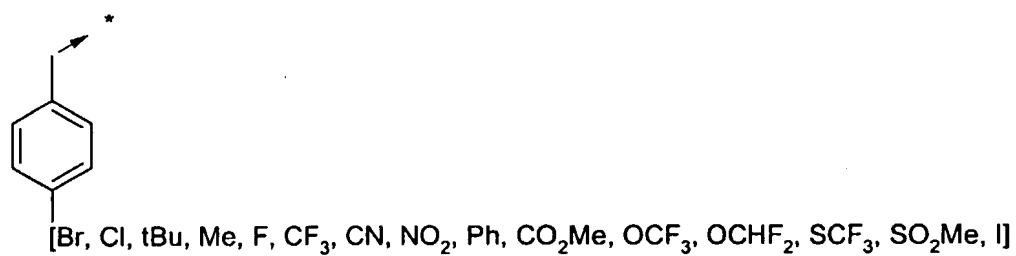
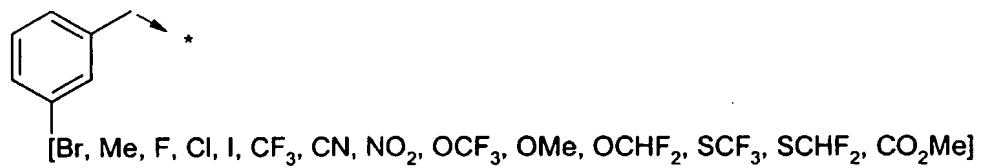
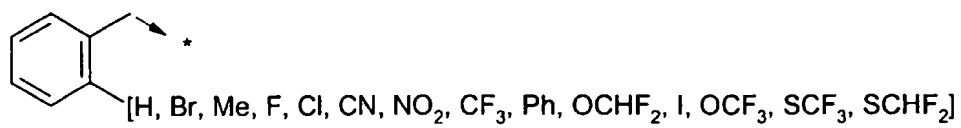
RMN 1H (CD_3OD , 400 MHz) δ : 7,65 (m, 2H); 7,40 (m, 2H); 7,31 (m, 1H); 7,20 (t, 1H); 7,10 (m, 1H); 7,06 (m, 2H); 4,04 (m, 1H); 3,68 (s, 3H); 3,60 (t, 2H); 3,04 (t, 2H); 2,94 (m, 2H); 2,29 (s, 3H); 2,14 (m, 2H); 1,91 (m, 2H); 1,76 (m, 2H). SM/CL : $m/z = 459,3$ ($M+H$).

Pour les groupes R_1 , X_1 , X_2 et X_3 tels qu'illustrés aux points A et B ci-dessus, les groupes R_3 que l'on peut envisager pour la synthèse de 4-aminopipéridines trisubstituées selon la procédure ci-dessus, sont les suivants :

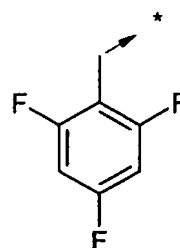
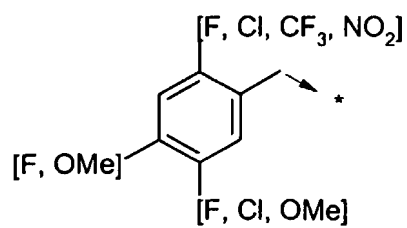
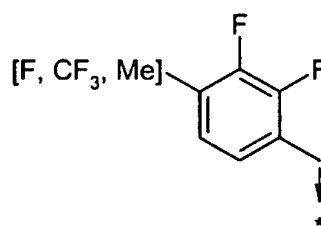
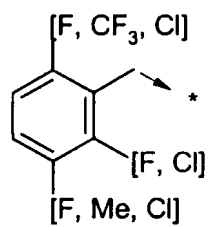
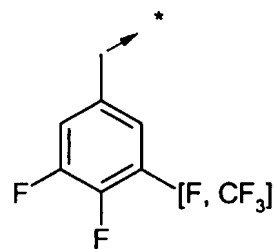
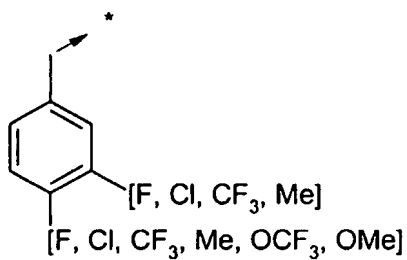
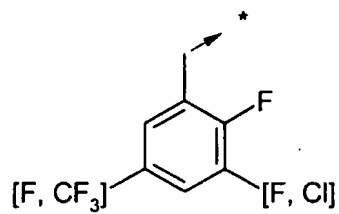
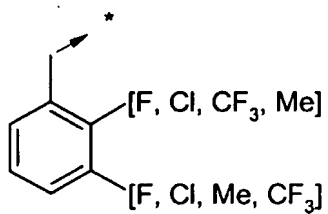
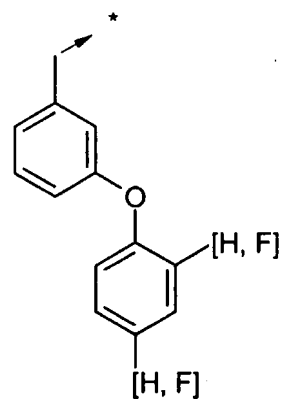
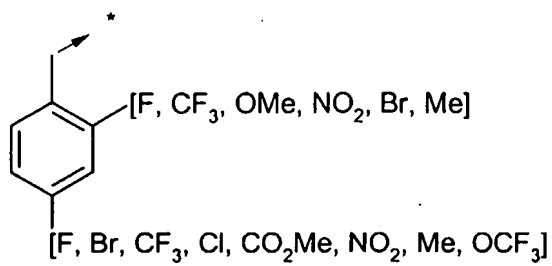
- 68 -



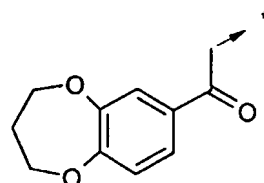
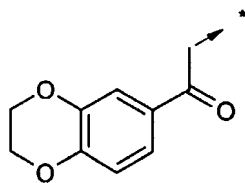
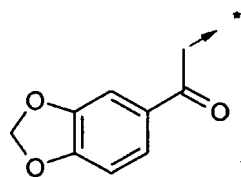
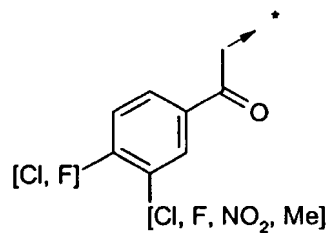
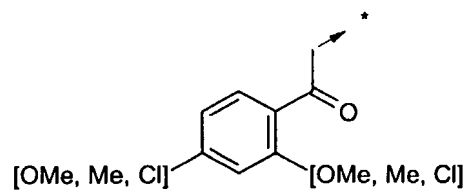
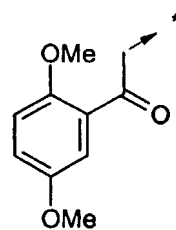
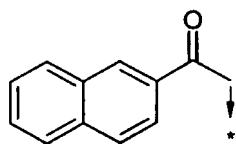
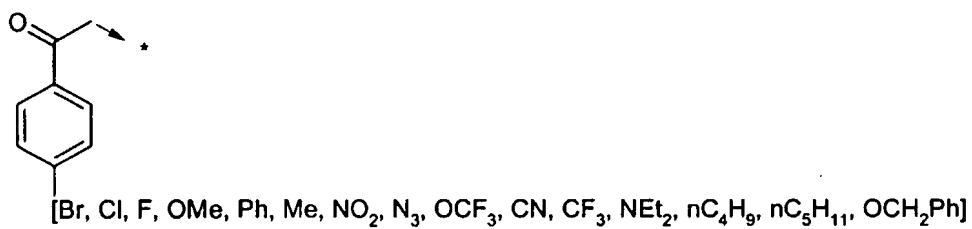
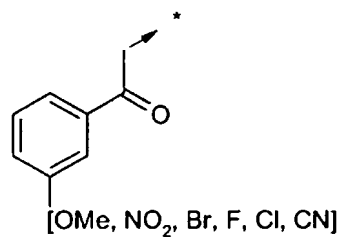
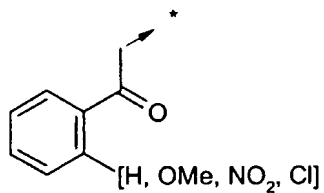
- 69 -



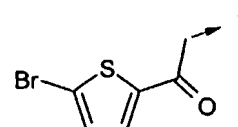
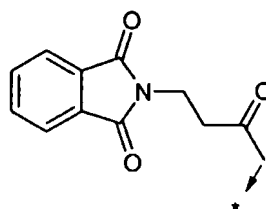
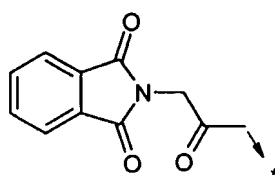
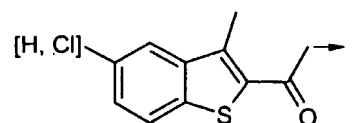
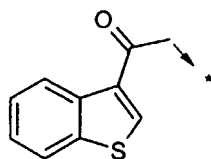
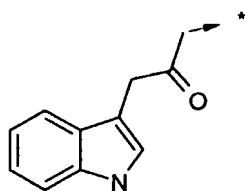
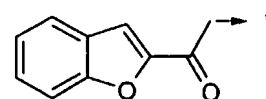
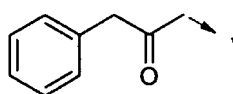
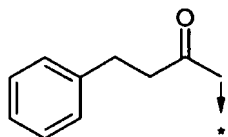
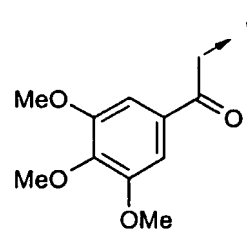
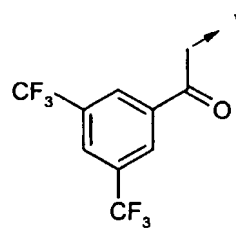
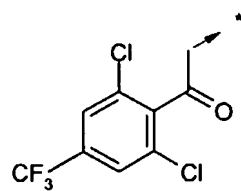
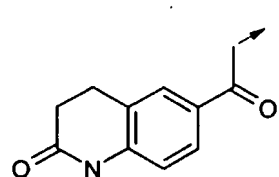
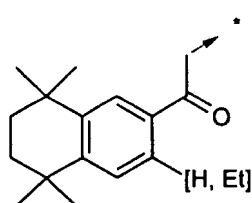
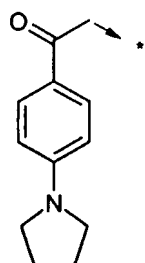
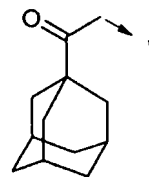
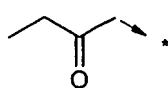
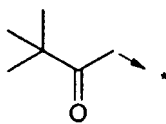
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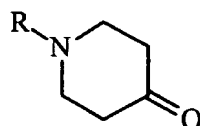


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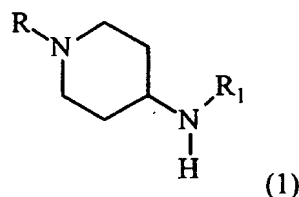
L'invention a également pour objet les procédés de préparation des composés I selon l'invention, en phase solide ou liquide, tels que décrits précédemment.

L'invention a plus particulièrement pour objet un procédé de préparation, en phase liquide, de composés de formule I telle que définie ci-dessus, caractérisé en ce qu'il
5 comprend

l'amination réductrice de la pipéridone N-substituée suivante

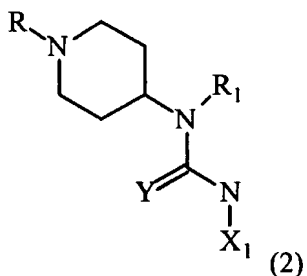


dans laquelle R représente le radical méthyle ou Boc, en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée ci-dessus, pour obtenir le
10 composé de formule 1



composé de formule (1) que l'on fait réagir avec

A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée ci-dessus, pour obtenir un composé de formule (2)



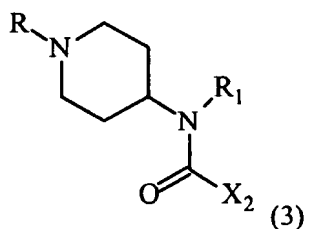
15

composé de formule (2) qui représente le composé de formule (I) correspondant dans lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à un traitement acide pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

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composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de
 formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1 , Y , X_2 et X_3 ont la
 signification indiquée ci-dessus, pour obtenir le composé de formule I correspondant
 dans laquelle R_2 représente un radical de formule $-C(Y)NHX_1$ et R_3 le radical $-C(Y)-$
 5 NHX_1 , $-C(O)X_2$ ou SO_2X_3 respectivement ;

B) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée
 ci-dessus, pour obtenir un composé de formule (3)

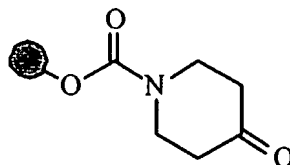


composé de formule (3) qui représente le composé de formule (I) correspondant dans
 10 lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à
 un traitement acide pour obtenir le composé de formule (I) correspondant dans
 laquelle R_3 représente l'atome d'hydrogène,

composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de
 formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1 , Y , X_2 et X_3 ont la
 15 signification indiquée ci-dessus, pour obtenir le composé de formule I correspondant
 dans laquelle R_2 représente un radical de formule $-C(O)X_2$ et R_3 le radical $-C(Y)-$
 NHX_1 , $-C(O)X_2$ ou SO_2X_3 respectivement.

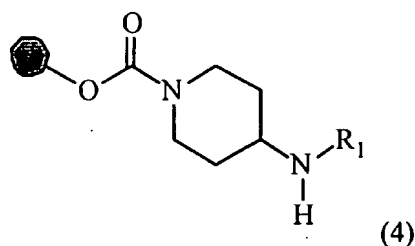
L'invention a plus particulièrement pour objet également un procédé de préparation,
 en phase solide, de composés de formule I telle que définie ci-dessus, caractérisé en
 20 ce qu'il comprend

l'amination réductrice de la résine cétonique



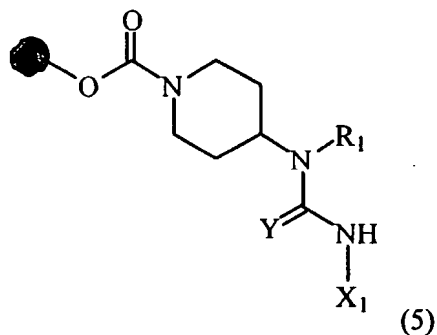
en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification
 indiquée ci-dessus, pour obtenir le composé de formule (4)

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composé de formule (4) que l'on fait réagir avec

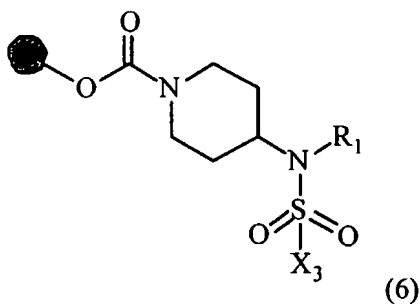
A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée ci-dessus, pour obtenir un composé de formule (5)



5

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée ci-dessus, pour obtenir un composé de formule (6)

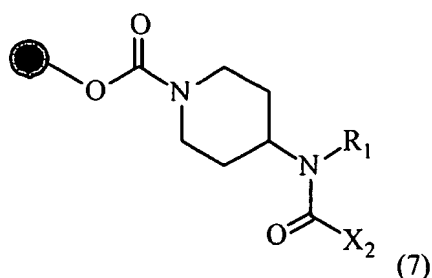


10

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (7)

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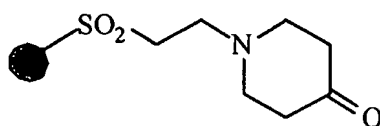


suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène ;

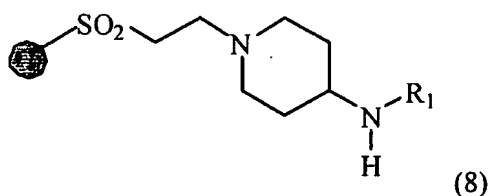
- D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (7) tel que défini ci-dessus, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène.

Enfin l'invention a plus particulièrement pour objet un procédé de préparation, en phase solide, de composés de formule I telle que définie ci-dessus, caractérisé en ce qu'il comprend

l'amination réductrice de la résine cétonique



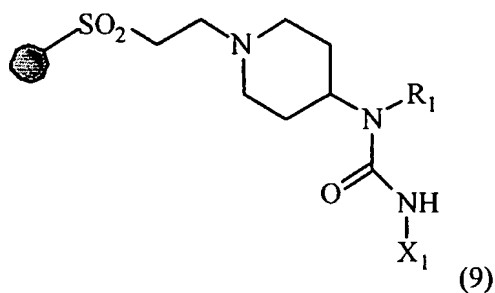
en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée ci-dessus, pour obtenir le composé de formule (8)



composé de formule (8) que l'on fait réagir avec

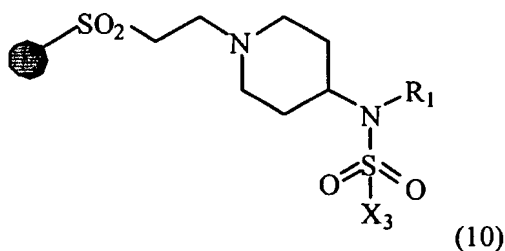
- A) soit un composé de formule $X_1NC(O)$ dans laquelle X_1 a la signification indiquée ci-dessus, pour obtenir un composé de formule (9)

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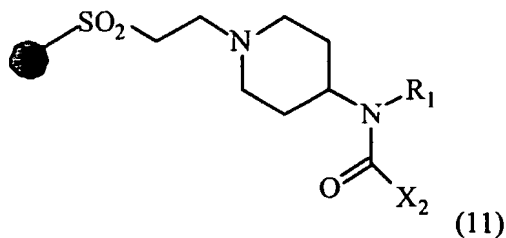
composé (9) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

- 5 B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée ci-dessus, pour obtenir un composé de formule (10)



- composé (10) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;
- 10

C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (11)



- composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;
- 15

D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée ci-dessus, pour obtenir un composé de formule (11) tel que défini ci-dessus,

composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini ci-dessus et X représente Br ou I, suivi du clivage de la
5 résine pour obtenir le composé de formule (I) correspondant.

Les composés I de la présente invention possèdent d'intéressantes propriétés pharmacologiques. C'est ainsi que l'on a découvert que les composés I de la présente invention ont une haute affinité pour un (ou plusieurs) des récepteurs de la somatostatine. Ils peuvent être utilisés comme agonistes ou antagonistes
10 non-peptidiques de la somatostatine de manière sélective ou non.

Les composés de la présente invention peuvent ainsi être utilisés dans différentes applications thérapeutiques. Ils peuvent avantageusement être utilisés pour traiter les états pathologiques ou les maladies tels que présentés ci-dessus et dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est(sont) impliqué(s).

15 On trouvera ci-après, dans la partie expérimentale, une illustration des propriétés pharmacologiques des composés de l'invention.

La présente demande a également pour objet, à titre de médicaments, les produits de formule I telle que définie ci-dessus, ainsi que les sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables desdits produits de
20 formule I, ainsi que les compositions pharmaceutiques contenant, à titre de principe actif, un au moins des médicaments tels que définis ci-dessus, en association avec un support pharmaceutiquement acceptable.

La composition pharmaceutique peut être sous forme d'un solide, par exemple, des poudres, des granules, des comprimés, des gélules ou des suppositoires. Les supports
25 solides appropriés peuvent être, par exemple, le phosphate de calcium, le stéarate de magnésium, le talc, les sucres, le lactose, la dextrine, l'amidon, la gélatine, la cellulose, la cellulose de méthyle, la cellulose carboxyméthyle de sodium, la polyvinylpyrrolidone et la cire.

Les compositions pharmaceutiques contenant un composé de l'invention peuvent
30 aussi se présenter sous forme liquide, par exemple, des solutions, des émulsions, des suspensions ou des sirops. Les supports liquides appropriés peuvent être, par exemple, l'eau, les solvants organiques tels que le glycérol ou les glycols, de même

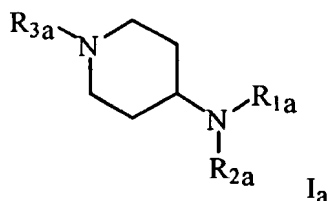
que leurs mélanges, dans des proportions variées, dans l'eau, additionnés à des huiles ou des graisses pharmaceutiquement acceptables. Les compositions liquides stériles peuvent être utilisées pour les injections intramusculaires, intrapéritonéales ou sous-cutanées et les compositions stériles peuvent également être administrée par

5 intraveineuse.

Certains composés de la formule générale I précédemment décrite sont couverts par la demande DE 2751138. Cette demande DE décrit des composés qui antagonisent les effets de la dopamine et des agents dopaminergiques endogènes ou exogènes et activent le mécanisme sérotoninergique, activités très différentes de celle décrite

10 dans la présente demande.

La présente invention a donc également pour objet l'utilisation des composés de formule générale I_a



sous forme racémique, d'énantiomère ou toutes combinaisons de ces formes, dans laquelle :

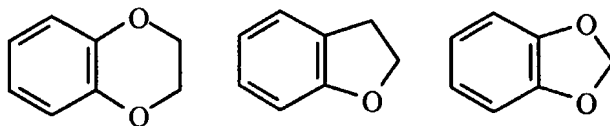
15 R_{1a} représente un radical (C₁-C₁₆)alkyle linéaire ou ramifié, alkényle, alkynyle, -(CH₂)_m-Y-Z₁₁ ou -(CH₂)_m-Z₁₂ dans lequel

Z₁₁ représente un (C₁-C₆)alkyle ou aryle éventuellement substitué,

Z₁₂ représente cyano, cyclohexényle, bis-phényle, (C₃-C₇)cycloalkyle, (C₃-C₇)hétérocycloalkyle éventuellement substitué, aryle éventuellement

20 substitué ou hétéroaryle éventuellement substitué,

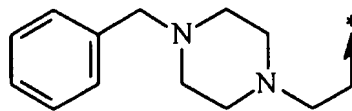
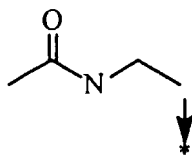
ou bien Z₁₂ représente un radical de formule



ou bien R_{1a} représente un radical de formule



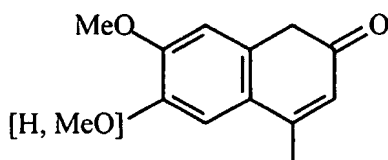
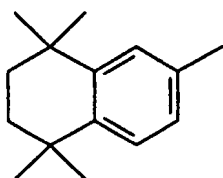
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R_{2a} représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 ;

R_{3a} représente l'atome d'hydrogène, un radical alkyle éventuellement substitué, alkényle, alkynyle, aralkyle éventuellement substitué, hétéroarylalkyle éventuellement substitué, ou un radical de formule $-C(Y)-NHX_1$, $-(CH_2)_n-C(O)X_2$,

5 SO_2X_3 ou

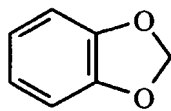
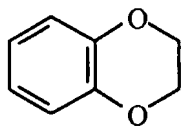


X_1 représente un radical (C_1-C_{15}) alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m-Y-Z_{21}$ ou $-(CH_2)_p-Z_{22}$ dans lequel

Z_{21} représente un (C_1-C_6) alkyle

10 Z_{22} représente cyclohexényle, indanyle, bis-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou aryle ou hétéroaryle éventuellement substitué,

ou Z_{22} représente un radical de formule



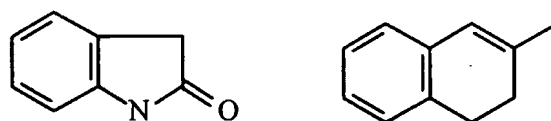
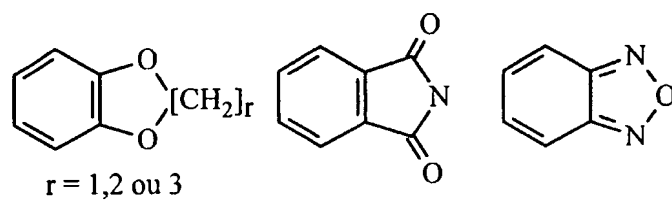
15 X_2 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), alkynyle, ou un radical de formule $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_p-U-Z_{24}$ dans lequel

Z_{23} représente un (C_1-C_6) alkyle ou aryle éventuellement substitué ;

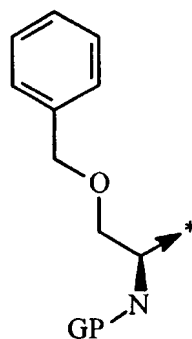
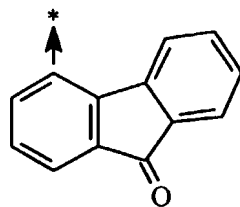
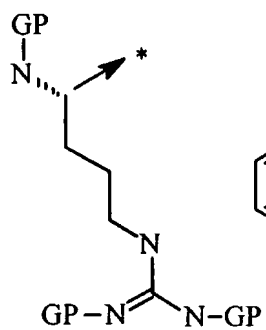
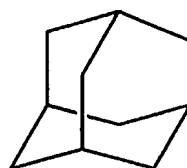
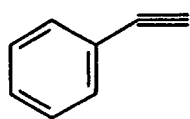
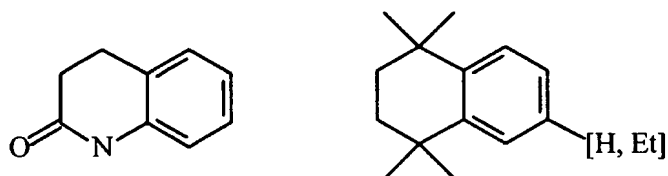
20 Z_{24} représente alkyle, cyclohexényle, bis-phényle, (C_3-C_7) cycloalkyle éventuellement substitué, (C_3-C_7) hétérocycloalkyle, cyano, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué,

ou Z_{24} représente un radical de formule

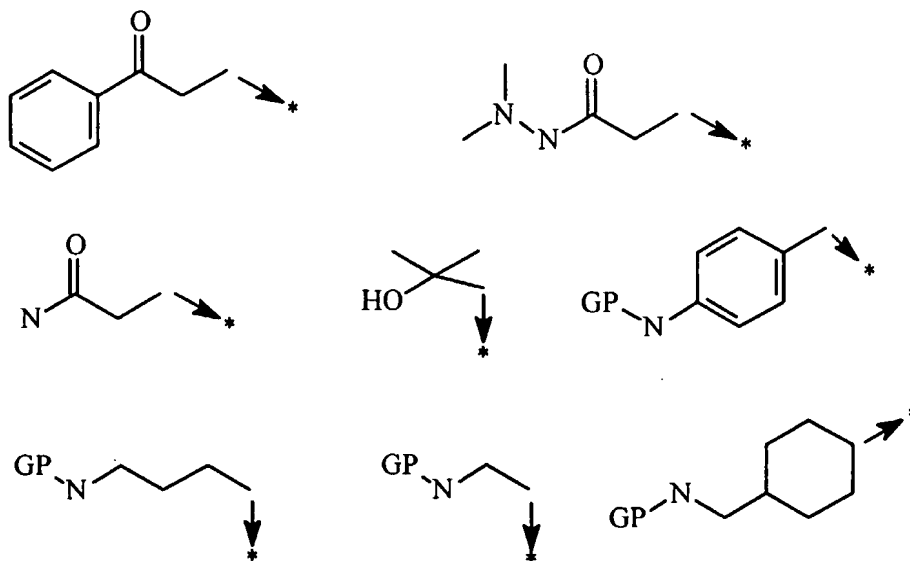
- 81 -



ou bien X_2 représente un radical représenté ci-dessous :



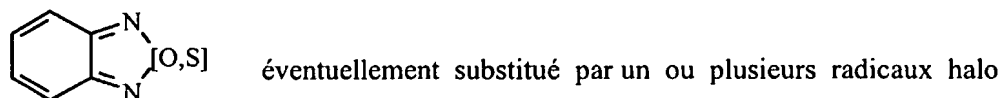
- 82 -



où le groupe protecteur (GP) représente H ou le *tert*-butyloxycarbonyl ;

X₃ représente un radical (C₁-C₁₀)alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), CF₃, ou -(CH₂)_pZ₂₅ dans lequel

Z₂₅ représente aryle ou hétéroaryle éventuellement substitué,
ou bien X₃ représente un radical de formule



identiques ou différents ;

Y représente un atome d'oxygène ou de soufre ;

10 W représente un atome d'oxygène, de soufre ou SO₂ ;

U représente une liaison covalente ou l'atome d'oxygène ;

n est un entier de 0 à 4 ;

m est un entier de 1 à 6 ;

p est un entier de 0 à 6 ;

15 q est un entier de 0 à 2,

ou leurs sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables, pour la préparation d'un médicament destiné à traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est (sont) impliqué(s).

- 5 L'invention a plus particulièrement pour objet l'utilisation des produits de formule générale I_a telle que définie ci-dessus, caractérisée en ce que

i) le ou les substituant(s) que peuvent porter les radicaux aryle que représentent Z_{11} et Z_{12} et hétéroaryle que représente Z_{12} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phényle, phénoxy, aminosulfonyle ;

ii) le ou les substituant(s) que peut porter le radical hétérocycloalkyle que représente Z_{12} sont choisis indépendamment parmi les radicaux oxy et alkyle ;

iii) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{22} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkényle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, aminosulfonyle, pipéridinosulfonyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, $-C(O)$ -alkyle, ou phényle, phénoxy, phénylthio, benzyloxy, le radical phényle pouvant être substitué ;

iv) le ou les substituant(s) que peut porter les radicaux aryle que représente Z_{23} et Z_{24} , cycloalkyle et hétéroaryle que représente Z_{24} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , $OCHF_2$, SCF_3 , nitro, cyano, azido, hydroxy, $-C(O)O$ -alkyle, $-O-C(O)$ -alkyle, $-NH-C(O)$ -alkyle, alkylsulfonyle, mono- ou di-alkylamino, amino, aminoalkyle, pyrrolyle, pyrrolydinyne ou bien les radicaux phényle, phénoxy, phénylthio, benzyle, benzyloxy dont le radical aryle est éventuellement substitué par un ou plusieurs radicaux alkyle, CF_3 ou halo ;

v) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{25} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , OCF_3 , nitro, cyano, $-NH-C(O)$ -alkyle, alkylsulfonyle, amino, mono- et di-alkylamino, phényle, pyridino ;

vi) le substituant que peut porter le radical alkyle que représente R_3 est le radical cyano.

vii) le ou les substituant(s) que peut porter le radical aralkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , OCF_3 , $OCHF_2$, SCF_3 , $SCHF_2$, nitro, cyano, $-C(O)O$ -alkyle, alkylsulfonyl, thiadiazolyle, ou bien les radicaux phényle et phénoxy dont le radical phényle est éventuellement substitué par un ou plusieurs radicaux halo.

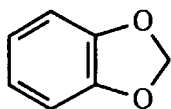
viii) le ou les substituant(s) que peut porter le radical hétéroarylalkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo ou nitro.

La présente invention a plus particulièrement pour objet l'utilisation des composés de formule générale I_a telle que définie ci-dessus, dans laquelle R_{1a} représente un radical (C_1-C_6) alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

Z_{11} représente un (C_1-C_6) alkyle,

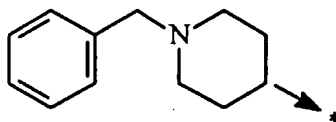
Z_{12} représente *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle éventuellement substitué, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy,

ou bien Z_{12} représente



Y représente l'atome d'oxygène,

ou bien R_{1a} représente un radical de formule

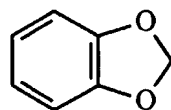


La présente invention a plus particulièrement pour objet l'utilisation des composés de formule générale I_a telle que définie ci-dessus, dans laquelle R_{2a} représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

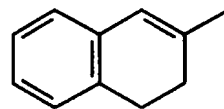
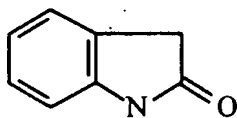
X_1 représente un radical (C_1-C_{15}) alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou

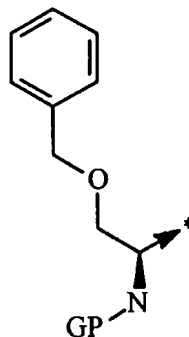
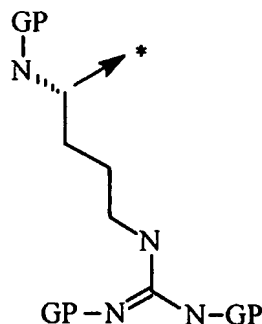
aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, pipéridinosulfonyl, $-\text{C}(\text{O})-\text{O}$ -alkyle, $-\text{C}(\text{O})$ -alkyle, ou phényle,
 5 ou bien Z_{22} représente un radical de formule



X_2 représente un radical $(\text{C}_1-\text{C}_{10})$ alkyle linéaire ou ramifié, alkynyle, $-(\text{CH}_2)_m-\text{W}-(\text{CH}_2)_q-\text{Z}_{23}$ ou $-(\text{CH}_2)_p-\text{U}-\text{Z}_{24}$ dans lequel
 W représente SO_2 ,
 U représente une liaison covalente,
 10 Z_{23} représente un radical aryle ;
 Z_{24} représente cyclohexényle, bis-phényle, (C_3-C_7) cycloalkyle éventuellement substitué par un radical aminoalkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-\text{CF}_3$, $-\text{OCF}_3$, SCF_3 ,
 15 hydroxy, $-\text{O}-\text{C}(\text{O})$ -alkyle, mono- ou di-alkylamino, amino
 ou Z_{24} représente un radical de formule



ou bien X_2 représente



20 X_3 représente un radical $-(\text{CH}_2)_p\text{Z}_{25}$ dans lequel Z_{25} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3 .

La présente invention a plus particulièrement pour objet l'utilisation des composés de formule générale I_a telle que définie ci-dessus, dans laquelle R_{3a} représente l'atome d'hydrogène, un radical alkyle, alkenyle, hétéroarylalkyle éventuellement substitué ou un radical de formule -C(Y)-NHX₁, -C(O)X₂ ou SO₂X₃ dans laquelle

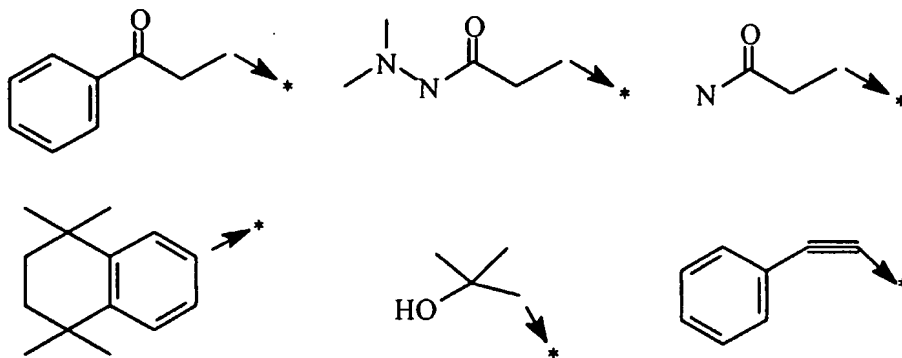
5 X₁ représente un radical -(CH₂)_pZ₂₂ dans lequel

Z₂₂ représente un radical aryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF₃, nitro, phénoxy ;

10 X₂ représente le radical vinyle substitué par un phényle, le radical phényle étant lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou -(CH₂)_p-U-Z₂₄ dans lequel

15 Z₂₄ représente alkyle, (C₃-C₇)cycloalkyle, (C₃-C₇)hétérocycloalkyle, bis-phényle, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, hydroxy, CF₃, nitro, amino, mono- et di-alkylamino, pyrrolyle,

ou bien X₂ représente un radical de formule



20 X₃ représente un radical (C₁-C₁₀)alkyle linéaire ou ramifié, le radical vinyle substitué par un radical (le radical phényle étant lui-même éventuellement substitué), CF₃, ou -(CH₂)_pZ₂₅ dans lequel

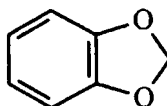
25 Z₂₅ représente aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF₃, nitro, -NH-C(O)-alkyle, mono- et di-alkylamino.

De manière préférentielle, R_{1a} représente un radical (C_1-C_6) alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

Z_{11} représente un (C_1-C_6) alkyle,

Z_{12} représente naphtyle, morpholino, *bis*-phényle, pyrrolidinyle substitué par le radical oxy, ou bien les radicaux phényle, pipérazinyle, pyridinyle et indolyle qui sont éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux bromo, fluoro, chloro, alkyle, alkoxy, $-CF_3$, $-OCF_3$;

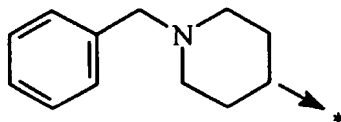
ou bien Z_{12} représente



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Y représente l'atome d'oxygène,

ou bien R_{1a} représente un radical de formule ci-dessous :



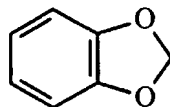
De manière préférentielle, R_{2a} représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

15

X_1 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

20

Z_{22} représente cyclohexyle, cyclohexényle, *bis*-phényle, morpholino, pipéridino, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou phényle, naphtyle ou furyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, pipéridinosulfonyl, $-C(O)-O$ -alkyle, $-C(O)$ -alkyle ou phényle, ou bien Z_{22} représente un radical de formule



25

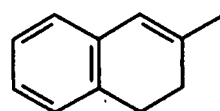
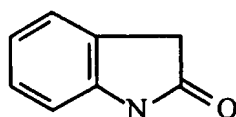
X_2 représente un radical alkyle, alkynyle, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_pZ_{24}$ dans lequel

W représente SO_2 ;

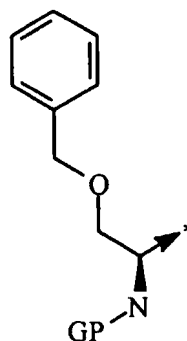
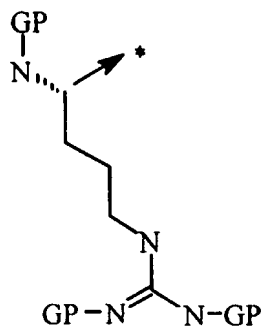
Z_{23} représente le radical phényle ;

Z_{24} représente cyclohexényle, bis-phényle, cyclohexyle éventuellement substitué par un radical aminoalkyle, ou phényle, naphthyle, benzothiényne, thiényne ou indolyle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-\text{CF}_3$, $-\text{OCF}_3$, SCF_3 , hydroxy, $-\text{O}-\text{C}(\text{O})$ -alkyle, $-\text{NH}-\text{C}(\text{O})$ -alkyle, mono- ou di-alkylamino, amino, ou

Z_{24} représente un radical de formule



ou bien X_2 représente



X_3 représente un radical $-(\text{CH}_2)_p Z_{25}$ dans lequel Z_{25} représente le radical phényle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3 ,

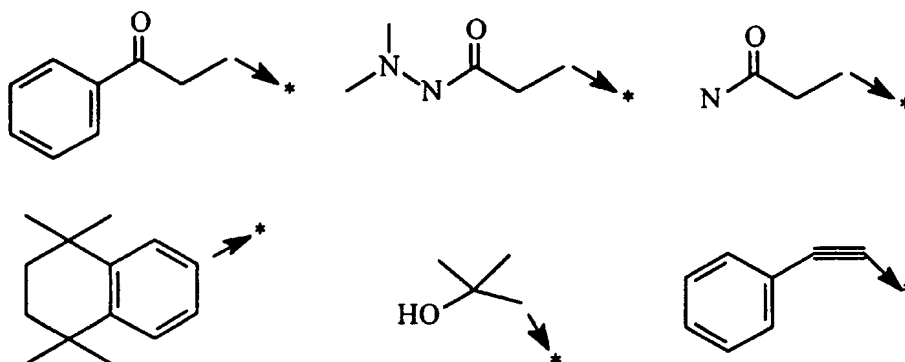
De manière préférentielle, R_{3a} représente l'atome d'hydrogène, un radical alkyle, alkenyle ou furyl-méthyl substitué par un ou plusieurs radicaux nitro, ou un radical de formule $-\text{C}(\text{Y})-\text{NHX}_1$, $-\text{C}(\text{O})\text{X}_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(\text{CH}_2)_p Z_{22}$ dans lequel

Z_{22} représente le radical phényle ou naphthyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, phénoxy,

X_2 représente le radical vinyle substitué par un radical phényle lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_p-U-Z_{24}$ dans lequel

- 5 Z_{24} représente alkyle, cyclohexyle, tétrahydrofuryle, *bis*-phényle, amino, mono ou di-alkylamino, ou phényle, indolyle, thiényle, pyridinyle, benzothiényne et furyle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, amino, mono- et di-alkylamino, nitro, hydroxy, pyrrolyle
ou bien X_2 représente un radical de formule



10

X_3 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, le radical vinyle substitué par un radical phényle, CF_3 , ou $-(CH_2)_p-Z_{25}$ dans lequel

- 15 Z_{25} représente un radical phényle, naphthyle, thiényle, pyrazolyle ou thiazolyle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, $-NH-C(O)-$ alkyle, mono- et di-alkylamino ;

De manière très préférentielle, R_{1a} représente le radical $-(CH_2)_m-Z_{12}$ dans lequel $m = 2$ et Z_{12} représente *bis*-phényle ou bien le radical indolyle substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux alkyle et alkoxy.

- 20 De manière très préférentielle, R_{2a} représente les radicaux de formule $-C(Y)NHX_1$ et $-C(O)X_2$ dans laquelle

Y représente S ;

X_1 représente un radical phényle éventuellement substitué par un ou plusieurs radicaux azido,

- 25 X_2 représente $-(CH_2)_p-Z_{24}$ dans lequel

p est égal à 1, 2 ou 3,

Z₂₄ représente cyclohexyle, ou phényle ou benzothiényne éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo ou -CF₃.

- 5 De manière très préférentielle, R_{3a} représente l'atome d'hydrogène ou le radical méthyle.

Tous les termes techniques et scientifiques utilisés dans le présent texte ont la signification connue de l'homme de l'art. Par ailleurs, tous les brevets (ou demandes de brevet) ainsi que les autres références bibliographiques sont incorporés par
10 référence.

Partie expérimentale :

D'autres composés selon l'invention obtenus selon les procédures des exemples A, B, C et D précédemment décrites, sont rassemblés dans le tableau ci-dessous.

- 15 Les composés sont caractérisés par leur temps de rétention (tr), exprimé en minute, et leur pic moléculaire (M+H⁺) déterminé par la spectroscopie de masse (SM).

Pour la spectroscopie de masse, un spectromètre de masse simple quadripôle (Micromass, modèle Platform) équipé d'une source électrospray est utilisé avec une résolution de 0,8 Da à 50 % de vallée. Les conditions pour les exemples 1 à 778 ci-dessous, sont les suivantes :

20 Conditions C1 et C2

Eluant : A : Eau + 0,02 % acide trifluoracétique ; B : acétonitrile

T (min)	A %	B %
0	100	0
1	100	0
10	15	85
12	15	85

Condition C1	Condition C2
Débit : 1,1 ml/min Injection : 5 µl Temp : 40° C Longueur d'ondes (% UV) : 210 nm Colonne : Uptisphere ODS 3 µm 33 * 4,6 mm i.d	Débit : 1,1 ml/min Injection : 20 µl Temp : 40° C Longueur d'ondes (% UV) : 210 nm Colonne : Kromasyl ODS 3,5 µm 50 * 4,6 mm i.d

Conditions C3

Eluant : A : Eau + 0,02 % acide trifluoracétique ; B : acétonitrile

5

T (min)	A %	B %
0	90	10
6	15	85
10	15	85

Débit : 1 ml/min

Injection : 5 µl

Colonne : Uptisphere ODS 3 µm 50 * 4,6 mm i.d

10

Temp : 40° C

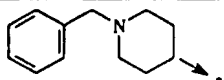
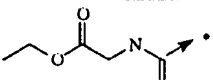
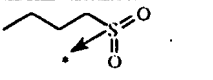
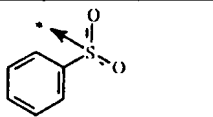
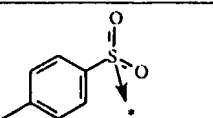
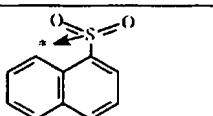
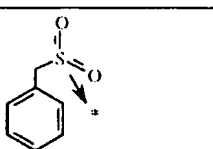
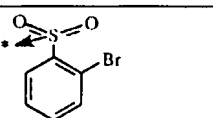
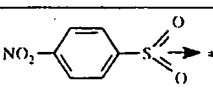
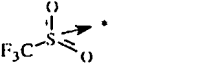
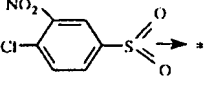
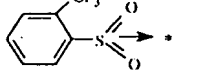
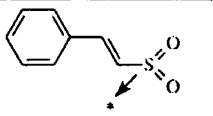
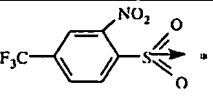
Longueur d'ondes (% UV) : 220 nm

Les conditions suivant les exemples, sont les suivantes :

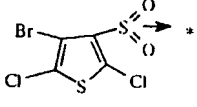
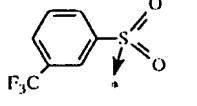
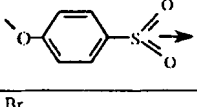
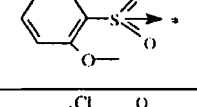
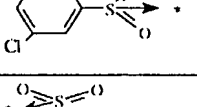
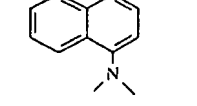
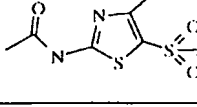
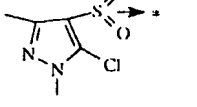
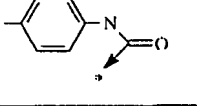
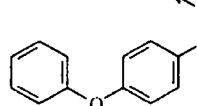
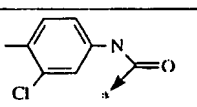
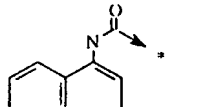
Exemples	Conditions
1 à 29	C2
30 à 263	C1
264 à 425	C3
426 à 456	C2
457 à 503	C3
504 à 586	C1
587 à 778	C3

Ces exemples sont présentés pour illustrer les procédures ci-dessus et ne doivent en aucun cas être considérés comme une limite à la portée de l'invention.

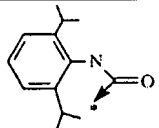
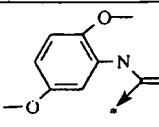
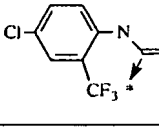
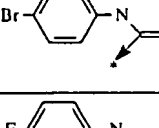
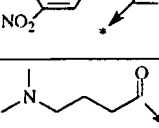
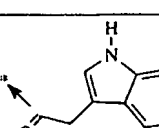
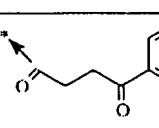
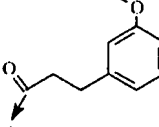
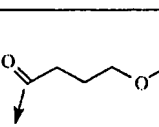
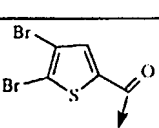
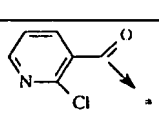

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Ex	R ₁	R ₂	R ₃	Pureté (en %)	tr	M+H+
1				66	7,6	523,3
2	"	"		94	7,7	543,2
3	"	"		96	8,1	557,2
4	"	"		98	8,5	593,2
5	"	"		95	7,8	557,2
6	"	"		97	8,1	623,1
7	"	"		95	8,1	588,2
8	"	"		19	8,1	535,2
9	"	"		99	8,5	622,2
10	"	"		80	8,4	611,2
11	"	"		99	8,2	569,2
12	"	"		93	8,9	656,2

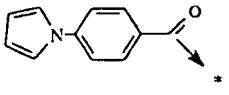
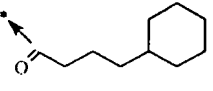
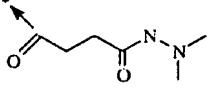
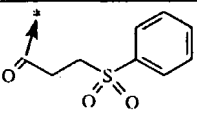
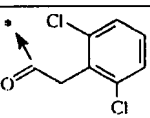
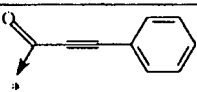
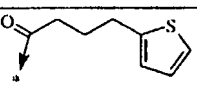
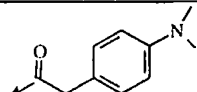
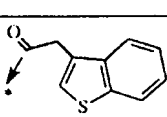
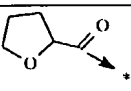
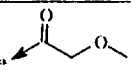
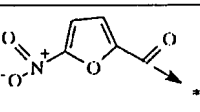
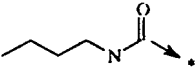
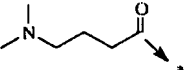
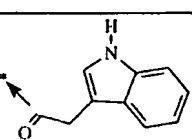
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13	"	"		85	9,1	697,0
14	"	"		95	8,7	611,2
15	"	"		87	7,8	573,2
16	"	"		100	8,4	653,2
17	"	"		97	8,6	611,1
18	"	"		99	8,7	636,3
19	"	"		83	7,2	621,2
20	"	"		98	7,4	595,2
21	"	"		84	7,4	536,3
22	"	"		99	8,4	614,3
23	"	"		63	8,2	570,2
24	"	"		92	7,5	572,3

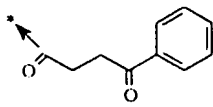
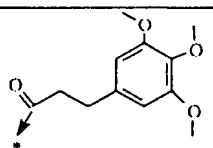
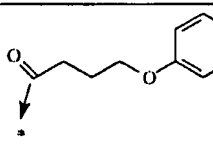
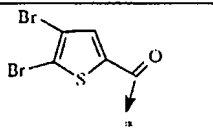
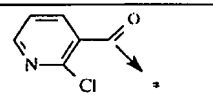
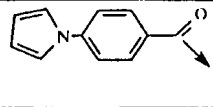
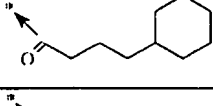
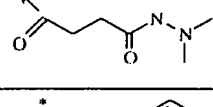
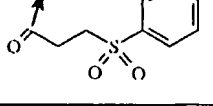
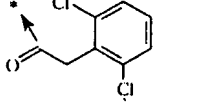
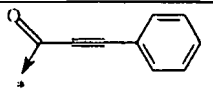
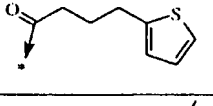
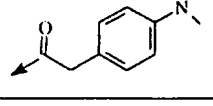
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25	"	"		93	8,4	606,4
26	"	"		96	7,4	582,3
27	"	"		93	8,1	624,2
28	"	"		93	7,8	602,2
29	"	"		95	7,4	585,2
30	"	"		87,39	4,0	516,4
31	"	"		92	5,5	560,3
32	"	"		90	5,7	563,3
33	"	"		87,73	5,6	625,4
34	"	"		85,41	6,0	565,4
35	"	"		98,4	6,4	671,1
36	"	"		86	4,9	542,3

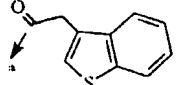
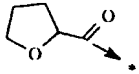
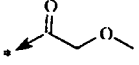
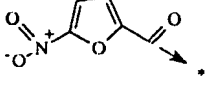
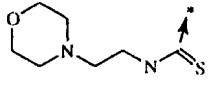
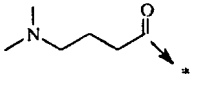
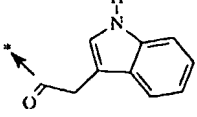
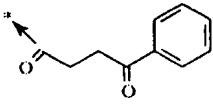
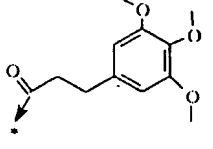
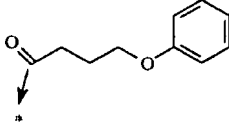
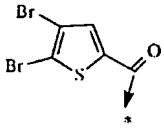
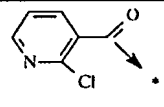
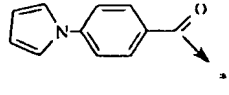
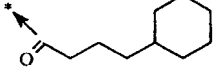
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37	"	"		89	6,1	572,3
38	"	"		77,61	6,8	555,4
39	"	"		89,16	4,2	545,4
40	"	"		92,32	5,3	599,3
41	"	"		83	6,0	589,2
42	"	"		36,3	5,9	531,2
43	"	"		83,27	5,9	555,3
44	"	"		82	4,5	564,4
45	"	"		86,75	6,0	577,3
46	"	"		91,95	4,7	501,4
47	"	"		88,94	4,5	475,3
48	"	"		73	5,3	542,3
49	"			90,96	4,4	486,4
50	"	"		95,5	5,9	530,4

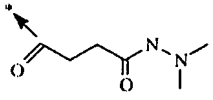
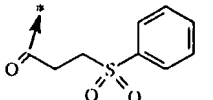
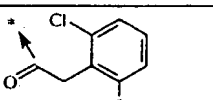
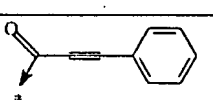
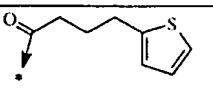
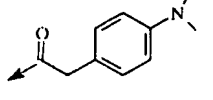
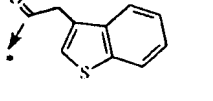
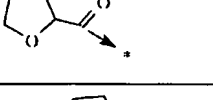
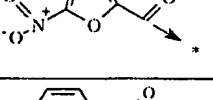
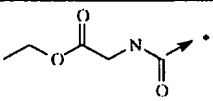
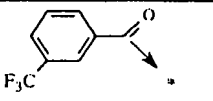
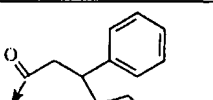
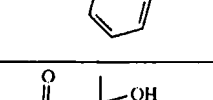
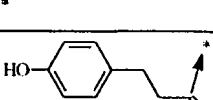
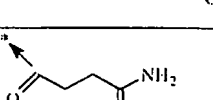
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51	"	"		94,51	6,1	533,4
52	"	"		93,64	6,0	595,4
53	"	"		96,05	6,5	535,4
54	"	"		84,68	6,9	641,1
55	"	"		86	5,5	512,3
56	"	"		92	6,5	542,4
57	"	"		91,29	7,2	525,5
58	"	"		94,7	4,7	515,4
59	"	"		94	5,8	569,3
60	"	"		89,43	6,6	559,3
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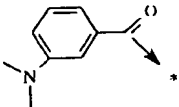
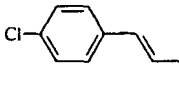
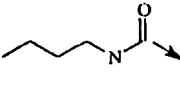
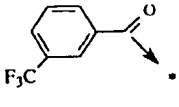
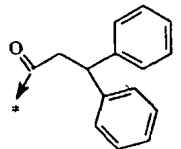
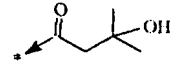
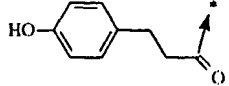
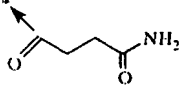
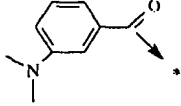
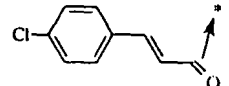
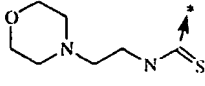
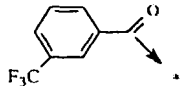
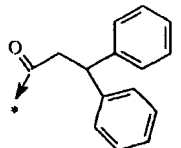
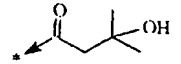
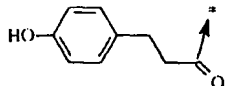
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64	"	"		94,32	6,4	547,3
65	"	"		91,71	5,2	471,4
66	"	"		92,47	5,0	445,4
67	"	"		58	5,9	512,3
68	"			84,55	3,6	559,4
69	"	"		87,7	4,7	603,4
70	"	"		90,77	4,8	606,4
71	"	"		72,34	4,8	668,4
72	"	"		87,18	5,1	608,4
73	"	"		69,52	5,4	714,1
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76	"	"		87,3	5,7	598,4

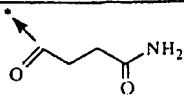
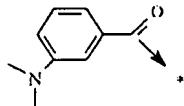
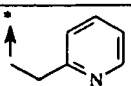
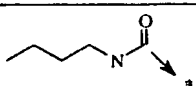
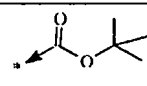
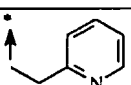
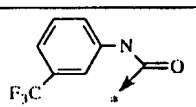
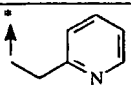
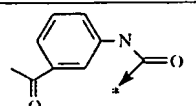
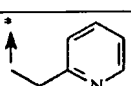
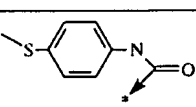
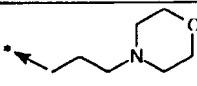
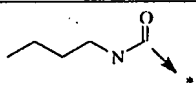
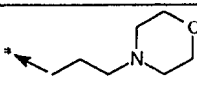
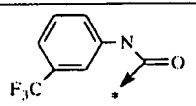
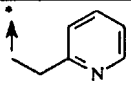
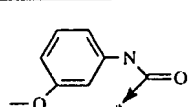
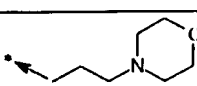
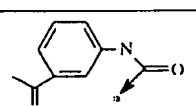
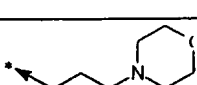
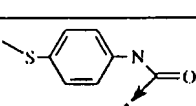
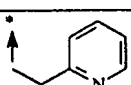
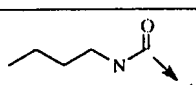

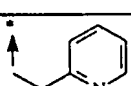
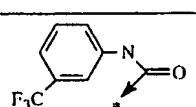
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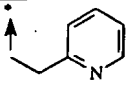
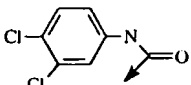
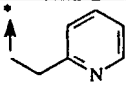
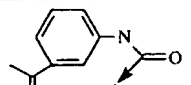
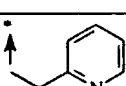
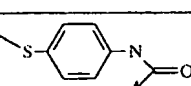
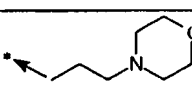
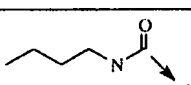
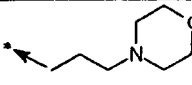
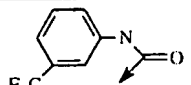
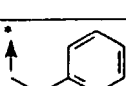
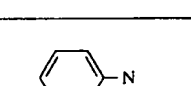
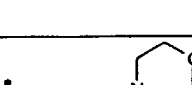
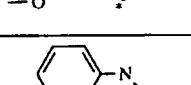
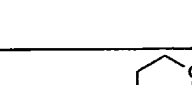

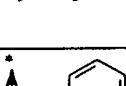
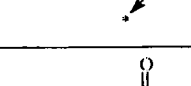
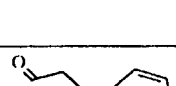
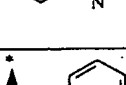
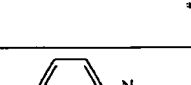
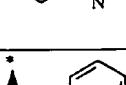

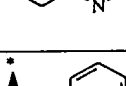

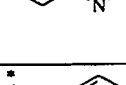

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78	"	"		89,9	4,5	642,3
79	"	"		61,5	5,1	632,3
80	"	"		43,65	5,0	574,3
81	"	"		88,18	5,0	598,3
82	"	"		88,6	4,0	607,4
83	"	"		90,08	5,1	620,3
84	"	"		85,57	4,0	544,3
85	"	"		48,41	4,5	585,3
86	"			82,68	6,1	589,3
87	"	"		79,99	6,5	611,4
88	"	"		86,07	4,8	503,4
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90	"	"		19,44	4,4	502,4

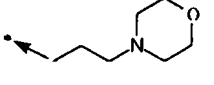
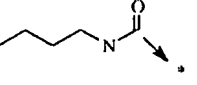
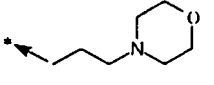
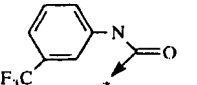
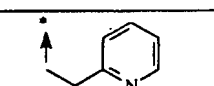
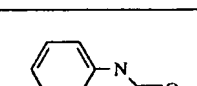
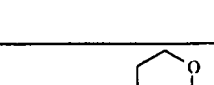
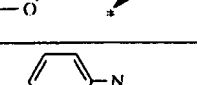
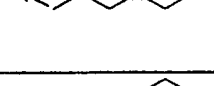

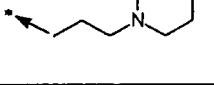
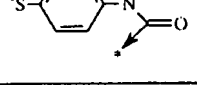
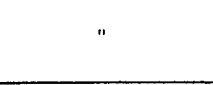
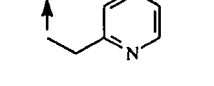
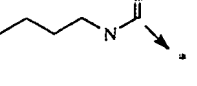
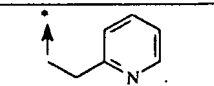
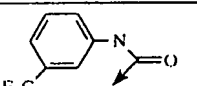
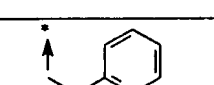
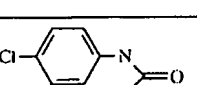
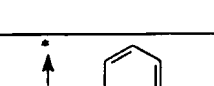
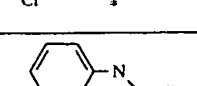
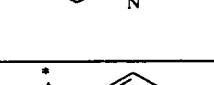

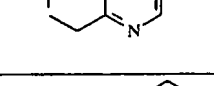
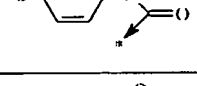
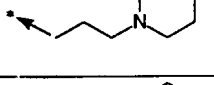
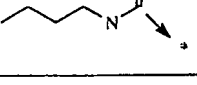
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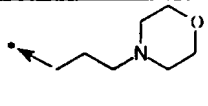
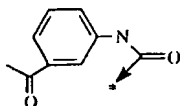
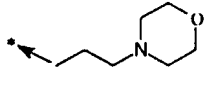
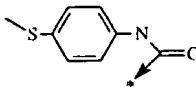
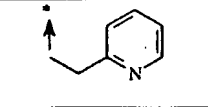
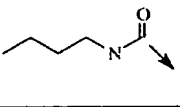
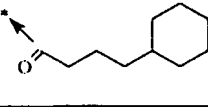
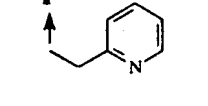
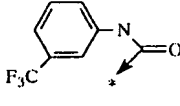
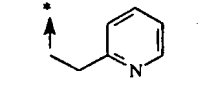
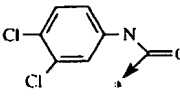
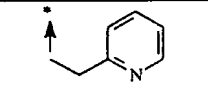
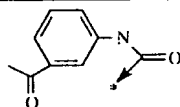
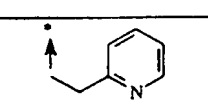
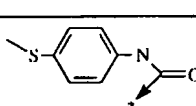
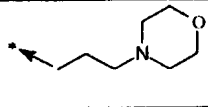
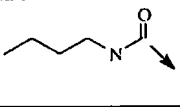
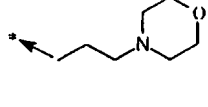
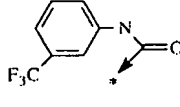
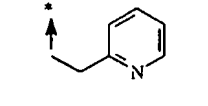
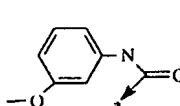
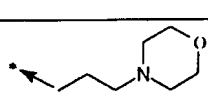
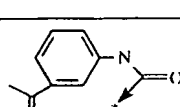
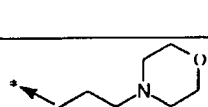
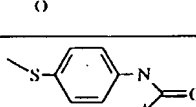
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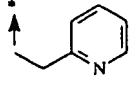
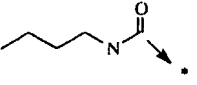
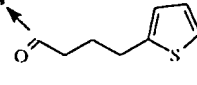
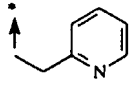
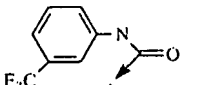
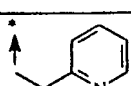
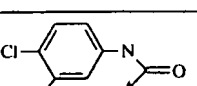
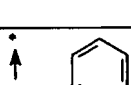
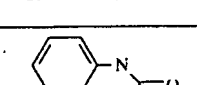
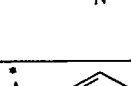

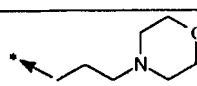
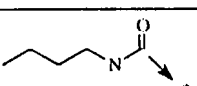
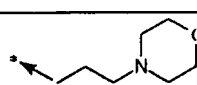
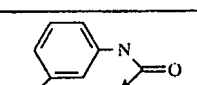

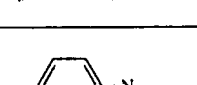
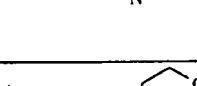
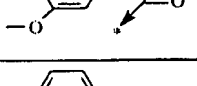
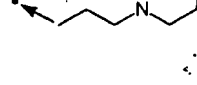
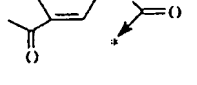
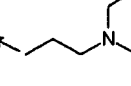
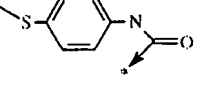
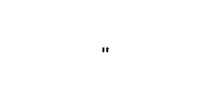
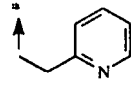
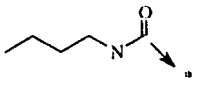
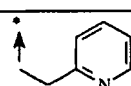
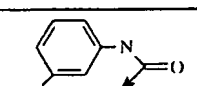
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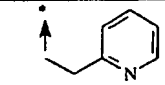
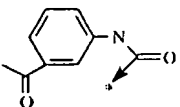
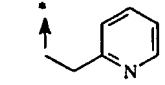
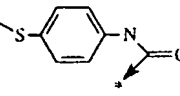
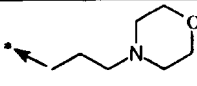
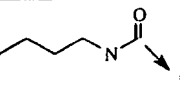
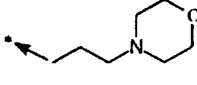
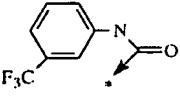
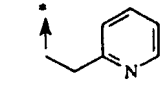
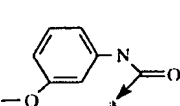
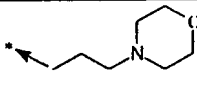
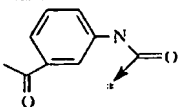
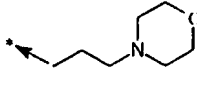
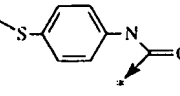
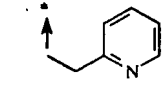
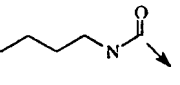
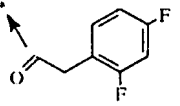
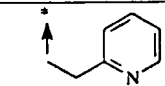
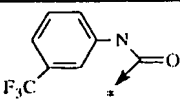
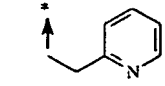
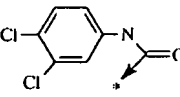
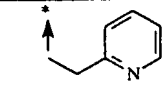
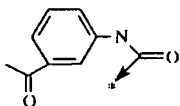
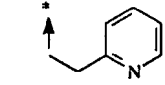
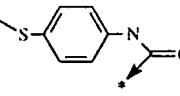
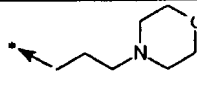
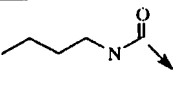
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106				69,62	5,9	405,2
107			"	98	7,1	493,2
108			"	80	6,0	467,3
109			"	88	6,5	471,2
110			"	60,04	5,7	427,3
111			"	78	6,5	515,2
112			"	97	6,2	455,2
113			"	70	5,7	489,3
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115				62,88	3,6	305,3
116			"	82,99	4,7	393,2

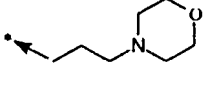
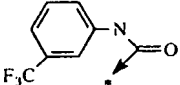
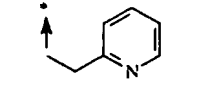
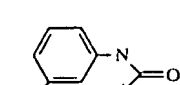
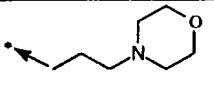
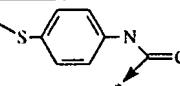
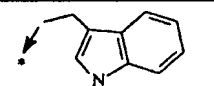
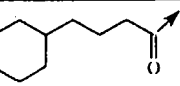
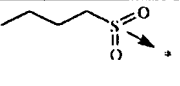
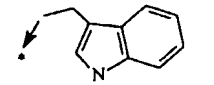
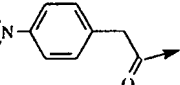
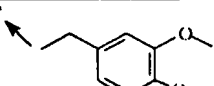
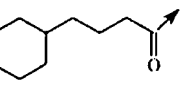
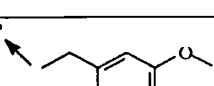
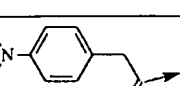
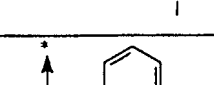
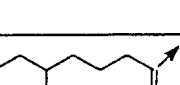
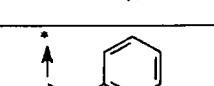
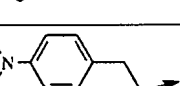
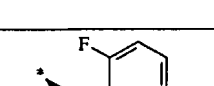
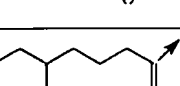
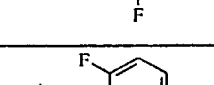
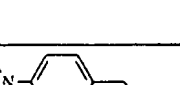
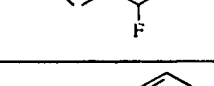
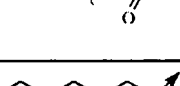
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118			"	10,53	5,4	367,3
119			"	74,79	4,3	371,2
120			"	50,14	3,4	327,3
121			"	70	4,3	415,2
122			"	84	3,9	355,3
123			"	66	3,5	389,3
124			"	94,61	3,9	393,2
125				71	5,5	462,3
126			"	52	6,6	550,2
127			"	57	6,8	550,1
128			"	60	5,6	524,2
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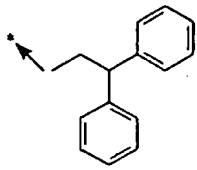
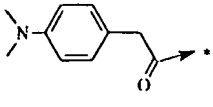
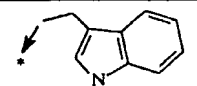
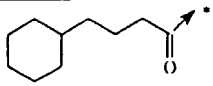
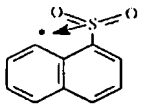
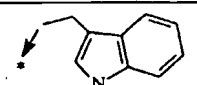
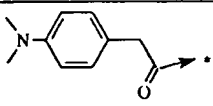
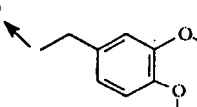
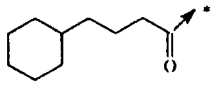
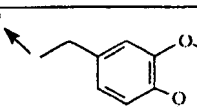
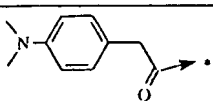
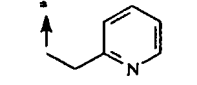
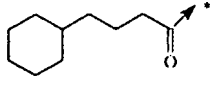
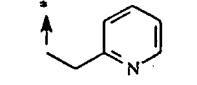
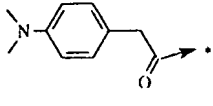
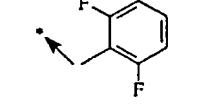
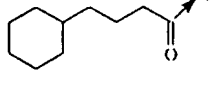
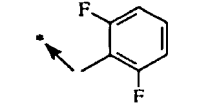
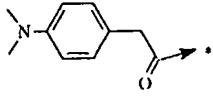
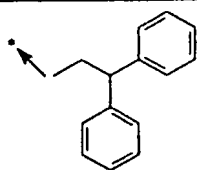
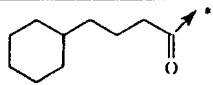
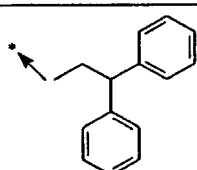
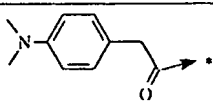
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135				76	5,3	483,3
136			"	49	6,4	571,2
137			"	63	6,6	571,1
138			"	79	5,4	545,2
139			"	57	5,9	549,2
140			"	66,58	5,2	505,3
141			"	61	6,0	593,2
142			"	67	5,5	533,2

143			"	61	5,2	567,3
144			"	51	5,6	571,2
145				56	7,0	457,3
146			"	64	8,1	545,2
147			"	52	8,3	545,2
148			"	69	7,1	519,3
149			"	70	7,6	523,3
150			"	63,77	6,7	479,4
151			"	50	7,3	567,3
152			"	46	7,3	507,3
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154			"	66	7,0	545,3

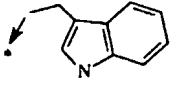
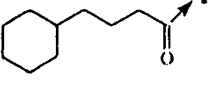
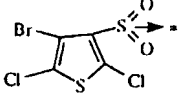
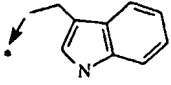
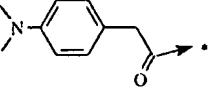
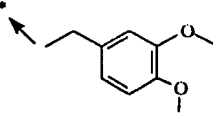
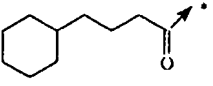
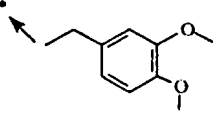
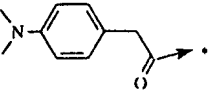
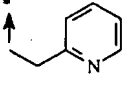
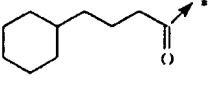
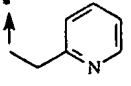
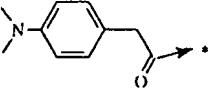
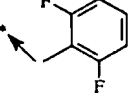
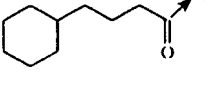
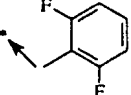
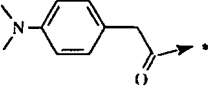
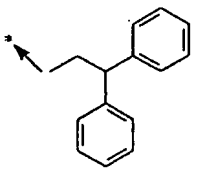
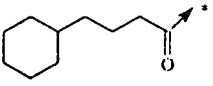
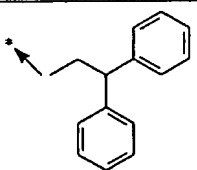
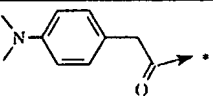
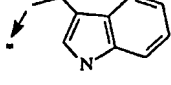
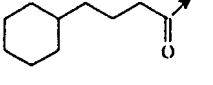
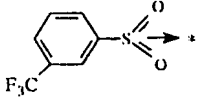
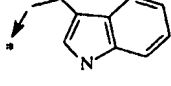
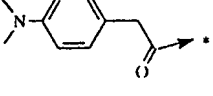
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157			"	67	7,3	545,1
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159			"	77	6,6	523,2
160			"	60,49	5,8	479,3
161			"	60	6,6	567,3
162			"	69	6,2	507,2
163			"	50	5,8	541,2
164			"	49	6,2	545,2
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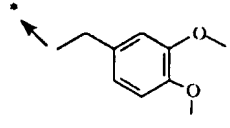
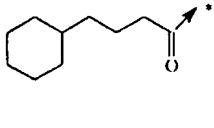
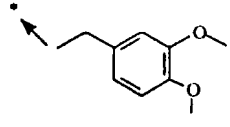
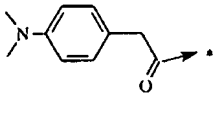
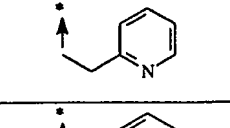
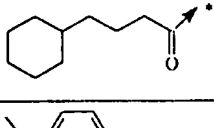
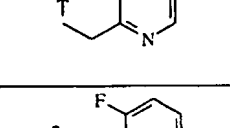
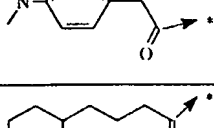
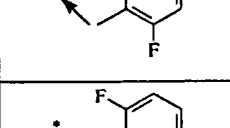
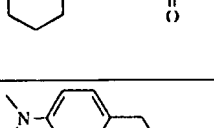
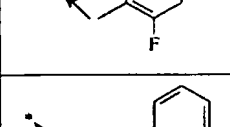
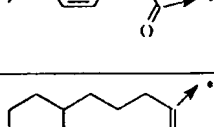
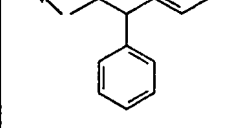
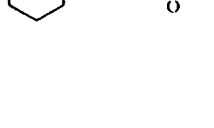
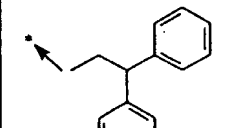
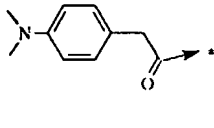
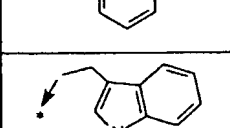
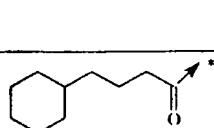
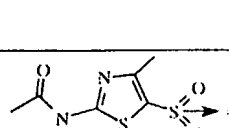
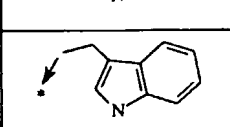
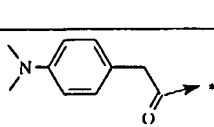
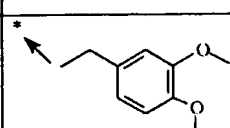
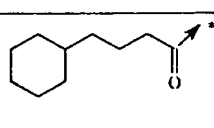
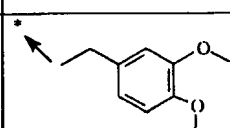
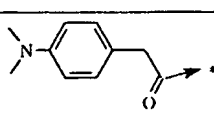
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171			"	55	5,2	576,3
172			"	50,35	4,7	516,3
173			"	7	5,2	550,3
174			"	48,63	4,8	554,3
175				53	5,7	459,2
176			"	49	6,9	547,2
177			"	61	7,1	547,1
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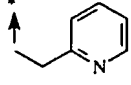
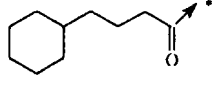
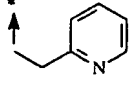
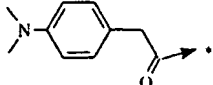
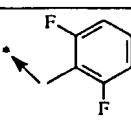
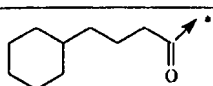
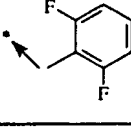
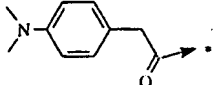
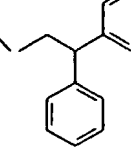
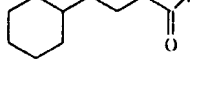
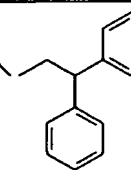
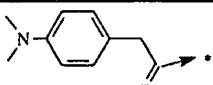
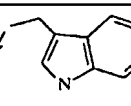
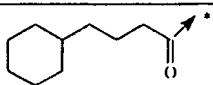
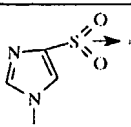
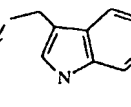
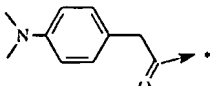
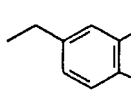
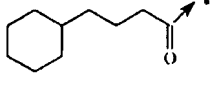
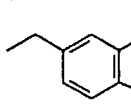
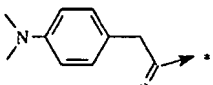
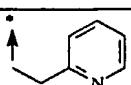
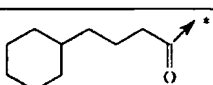
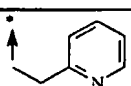
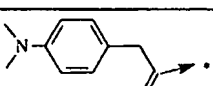
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182			"	64	6,0	509,2
183			"	63	6,0	547,2
184				67,83	10,1	516,3
185			"	61,66	6,7	525,3
186			"	40,48	9,9	537,3
187			"	50	6,4	546,3
188			"	42,57	7,4	478,4
189			"	29	4,8	487,3
190			"	55	10,3	499,3
191			"	19,39	6,7	508,3
192			"	67	11,1	567,3

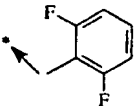
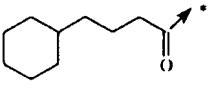
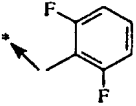
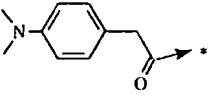
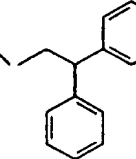
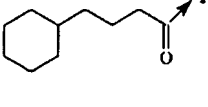
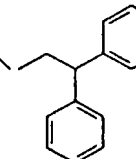
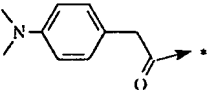
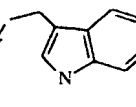
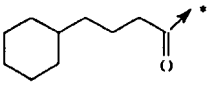
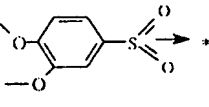
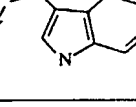
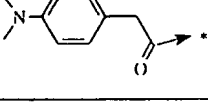
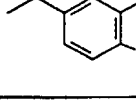
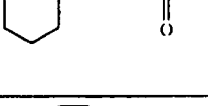
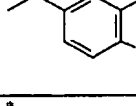
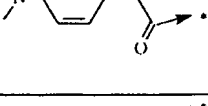
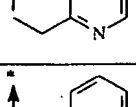
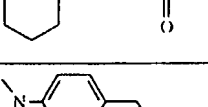
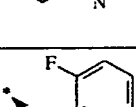
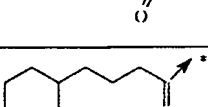
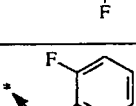
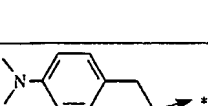
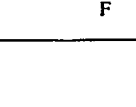
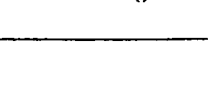
193			"	64,73	7,9	576,3
194				92	10,6	586,3
195			"	85	7,3	595,3
196			"	96	10,5	607,3
197			"	89,25	7,2	616,3
198			"	98,24	7,9	548,3
199			"	94	5,6	557,3
200			"	98	10,8	569,2
201			"	93,17	7,3	578,2
202			"	97,82	11,7	637,3
203			"	88,11	8,5	646,3

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204				73	11,2	690,0
205			"	60,44	7,9	699,0
206			"	76	11,1	711,0
207			"	72,2	7,8	720,0
208			"	89,42	8,5	652
209			"	48	6,2	659,0
210			"	78,2	11,6	673,0
211			"	66,1	7,9	682,0
212			"	78	12,6	739,1
213			"	88,77	9,1	750,0
214				73	10,6	604,3
215			"	67	7,5	613,2

216			"	73	10,5	625,3
217			"	83	7,3	634,2
218			"	87,32	7,9	566,3
219			"	79	5,7	575,2
220			"	89	10,7	587,2
221			"	78,75	7,4	596,2
222			"	95	11,6	655,3
223			"	79	8,6	664,3
224				58	9,4	614,2
225			"	78	6,4	623,2
226			"	75	9,2	635,3
227			"	88	6,1	644,3

228			"	86	6,7	576,3
229			"	80	4,6	585,2
230			"	73	9,5	597,2
231			"	66	6,2	606,2
232			"	62	10,5	665,3
233			"	81	7,5	674,3
234				92	8,9	540,3
235			"	86	5,6	549,2
236			"	91	8,7	561,3
237			"	94,51	5,4	570,2
238			"	93,36	6,2	502,3
239			"	97	3,8	511,3

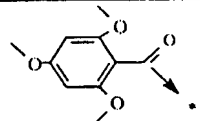
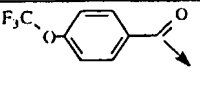
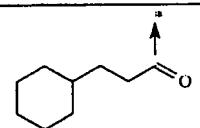
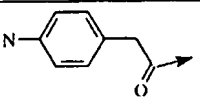
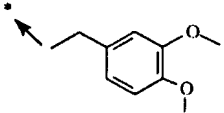
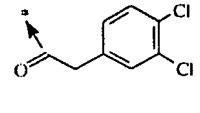
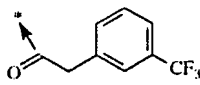
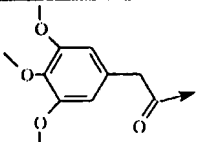
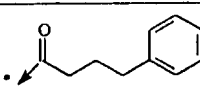
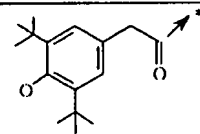
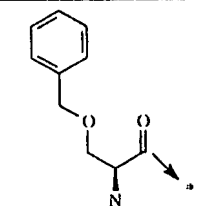
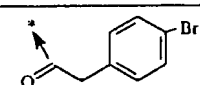
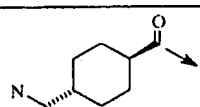
240			"	98,13	9,0	523,3
241			"	82	5,4	532,2
242			"	99	10,1	591,3
243			"	94,74	6,8	600,3
244				89	9,8	596,3
245			"	81	6,6	605,3
246			"	96	9,7	617,3
247			"	85,68	6,4	626,3
248			"	98,65	7,1	558,3
249			"	92	4,8	567,2
250			"	96	10,0	579,2
251			"	88,12	6,5	588,2

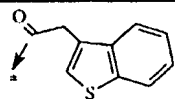
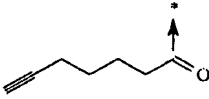
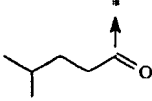
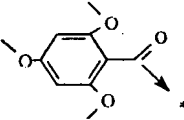
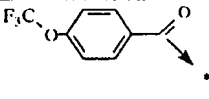
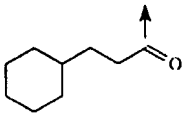
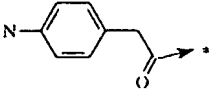
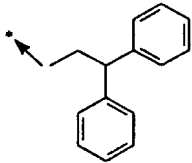
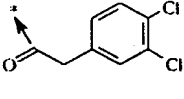
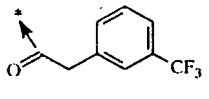
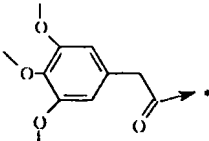
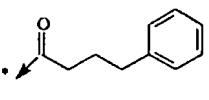
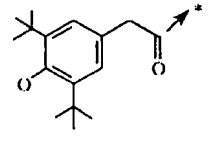
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252			"	97	10,9	647,3
253			"	86	7,8	656,3
254				79	10,1	572,2
255			"	79	7,0	581,2
256			"	71	10,0	593,3
257			"	72,74	6,6	602,2
258			"	79,1	7,4	534,3
259			"	74	4,9	543,2
260			"	84,17	10,3	555,2
261			"	76,16	6,7	564,2
262			"	95	11,1	623,3

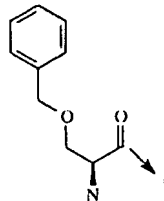
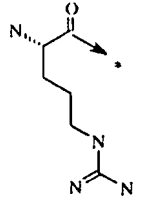
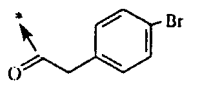
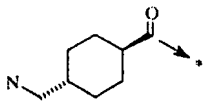
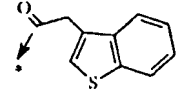
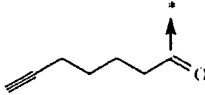
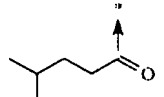
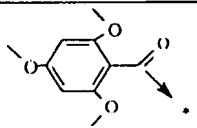
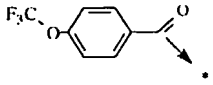
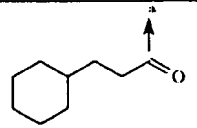
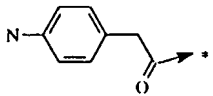
263			"	78,91	8,0	632,3
264			H → "	75,26	5,1	430,2
265	"		"	90,43	5,0	430,3
266	"		"	74,93	4,3	452,3
267	"		"	79,62	4,9	390,3
268	"		"	92,82	5,6	490,4
269	"		"	68,87	3,6	421,3
270	"		"	79,07	4,9	440,2
271	"		"	84,22	3,0	392,3
272	"		"	67,34	4,9	418,2
273	"		"	81,63	4,4	352,3
274	"		"	90,11	4,7	342,3

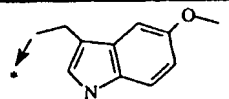
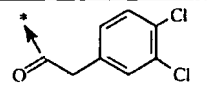
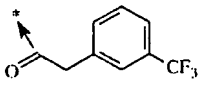
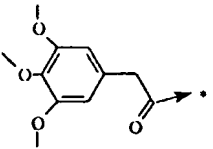
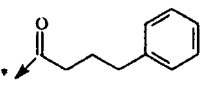
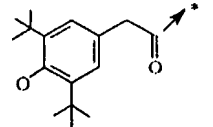
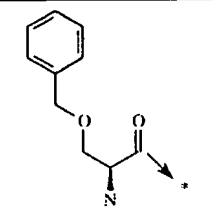
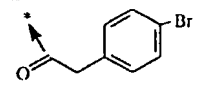
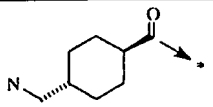
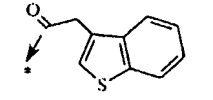
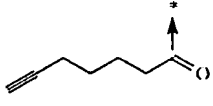
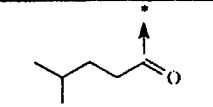
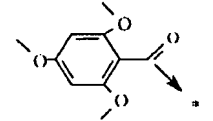
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275	"		"	54,36	4,3	438,3
276	"		"	81,69	4,9	432,2
277	"		"	85,62	5,2	382,3
278	"		"	86,19	3,2	377,3
279			"	94,76	4,9	451,2
280	"		"	99,42	4,7	451,3
281	"		"	90,55	4,0	473,3
282	"		"	93,80	4,6	411,3
283	"		"	82,71	5,4	511,4
284	"		"	90,85	3,4	442,3
285	"		"	98,65	4,6	461,2
286	"		"	98,80	2,8	404,3

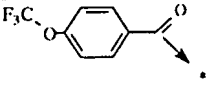
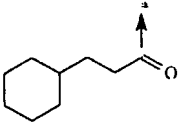
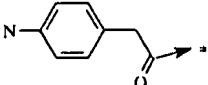
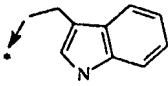
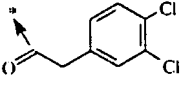
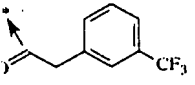
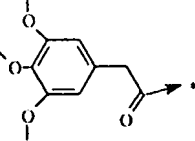
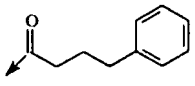
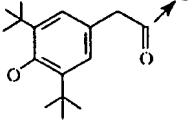
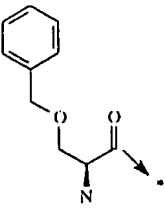
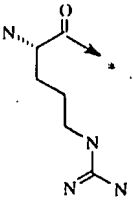
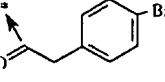
287	"		"	86.02	4,6	439,3
288	"		"	97,47	4,1	373,3
289	"		"	99,31	4,4	363,3
290	"		"	45,77	4,1	459,3
291	"		"	94,07	4,6	453,3
292	"		"	95,65	5,0	403,4
293	"		"	94,30	2,9	398,3
294			"	80,64	5,9	481,2
295	"		"	98,05	5,7	481,3
296	"		"	94,93	5,0	503,4
297	"		"	96,81	5,6	441,3
298	"		"	95,00	6,3	541,4

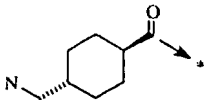
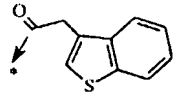
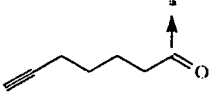
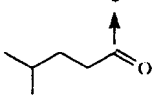
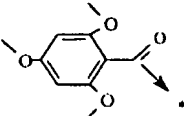
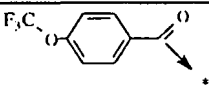
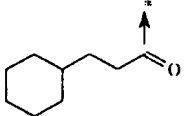
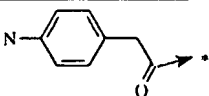
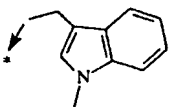
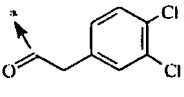

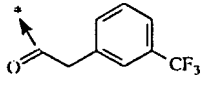
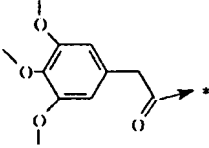
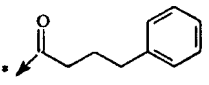
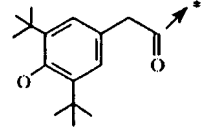
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299	"		"	95,13	4,2	472,4
300	"		"	52,68	3,2	452,4
301	"		"	98,03	5,6	491,2
302	"		"	96,44	3,7	217,9
303	"		"	97,22	5,6	469,3
304	"		"	96,97	5,2	403,3
305	"		"	99,05	5,4	393,4
306	"		"	32,67	5,1	489,3
307	"		"	84,51	5,6	483,3
308	"		"	98,44	6,0	433,4
309	"		"	97,78	4,0	428,3

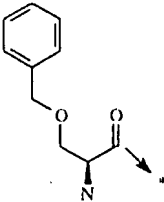
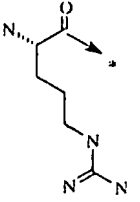
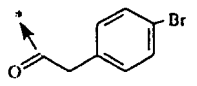
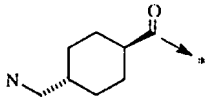
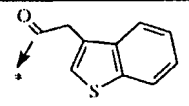
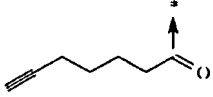
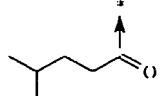
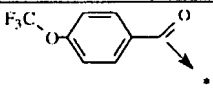
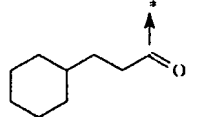
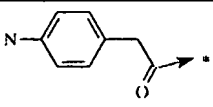
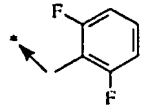
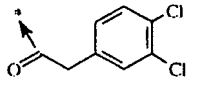
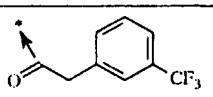
310			"	79,54	5,0	460,2
311	"		"	78,59	4,9	460,3
312	"		"	66,24	4,2	482,3
313	"		"	70,15	4,8	420,3
314	"		"	57,87	5,5	520,4
315	"		"	71,26	3,6	451,3
316	"		"	81,16	4,8	470,2
317	"		"	74,96	2,9	413,3
318	"		"	53,47	4,8	448,3
319	"		"	87,88	4,3	382,3
320	"		"	91,41	4,6	372,3
321	"		"	1,59	5,0	468,3

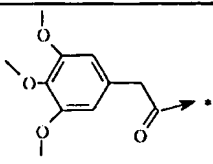
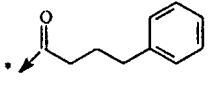
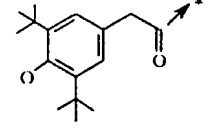
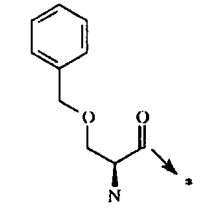
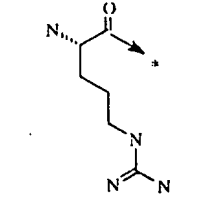
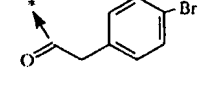
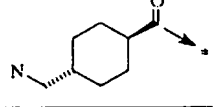
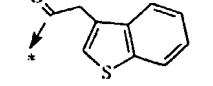
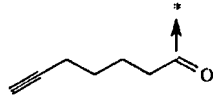
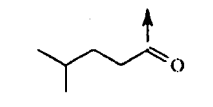
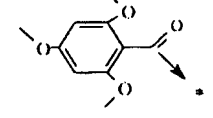
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322	"		"	77,81	4,8	462,3
323	"		"	76,59	5,1	412,3
324	"		"	83,35	3,1	407,3
325			$\text{CH}_3 \rightarrow *$	87,42	5,2	444,2
326	"		"	98,89	5,1	444,3
327	"		"	95,68	4,3	466,3
328	"		"	97,27	4,9	404,3
329	"		"	95,73	5,7	504,4
330	"		"	83,37	3,7	435,3
331	"		"	71,88	3,2	413,3
332	"		"	98,33	5,0	454,2

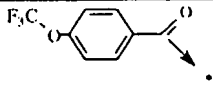
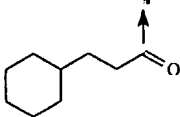
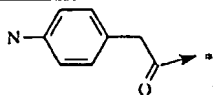
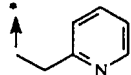
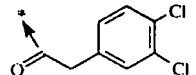
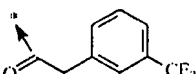
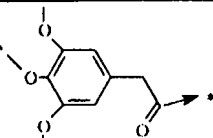
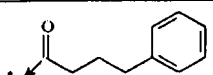
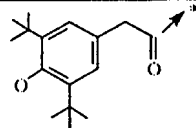
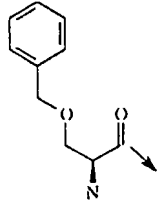
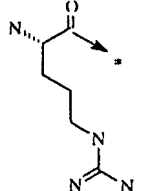
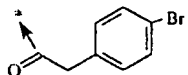
333	"		"	83,73	3,0	397,3
334	"		"	94,77	5,0	432,3
335	"		"	95,88	4,5	366,3
336	"		"	98,9	4,7	356,3
337	"		"	50,74	4,4	452,3
338	"		"	95,39	5,0	446,3
339	"		"	98,2	5,3	396,3
340	"		"	92,35	3,2	391,3
341			H 	90,41	5,1	444,2
342	"		"	87,41	5,0	444,3
343	"		"	87,37	4,3	466,3
344	"		"	83,01	4,9	404,3
345	"		"	89,47	5,6	504,4

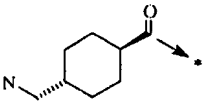
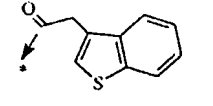
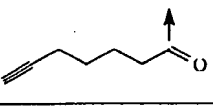
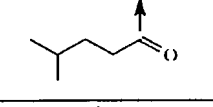
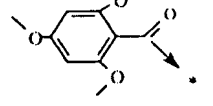
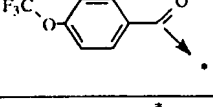
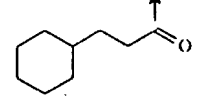
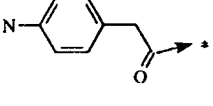
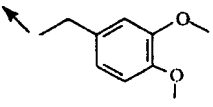
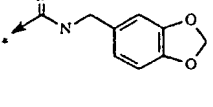
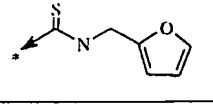
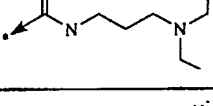
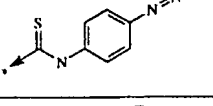
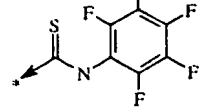
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346	"		"	77.55	3,6	435,3
347	"		"	49.49	2,4	414,3
348	"		"	85.63	4,9	454,2
349	"		"	88.12	2,9	397,3
350	"		"	87.73	4,9	432,3
351	"		"	84.48	4,4	366,3
352	"		"	82.03	4,7	356,3
353	"		"	82.93	4,9	446,3
354	"		"	72.6	5,3	396,3
355	"		"	86.75	3,2	391,3
356			"	93.75	4,7	413,1
357	"		"	96.13	4,6	413,2

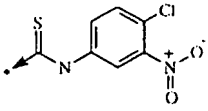
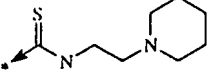
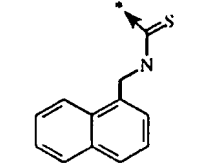
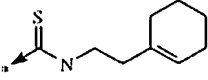
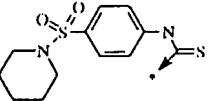
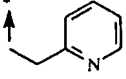
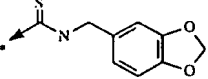
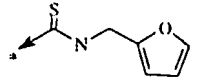
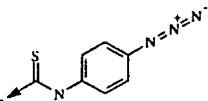
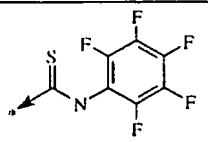
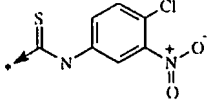
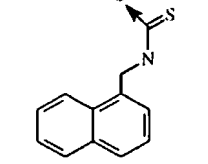
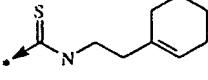
358	"		"	98,3	3,8	435,2
359	"		"	96,45	4,5	373,2
360	"		"	97,9	5,3	473,4
361	"		"	97,57	3,0	404,3
362	"		"	78,0	2,5	383,2
363	"		"	98,96	4,5	423,1
364	"		"	93,98	2,4	366,3
365	"		"	97,98	4,5	401,2
366	"		"	93,33	4,0	335,2
367	"		"	95,73	4,3	325,3
368	"		"	1,21	3,9	421,3

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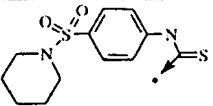
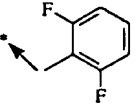
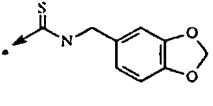
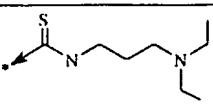
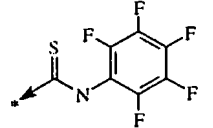
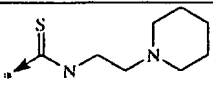
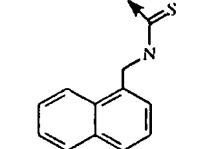
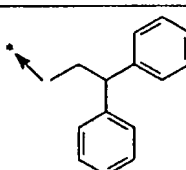
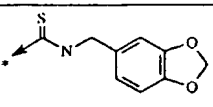
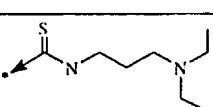
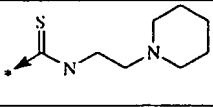
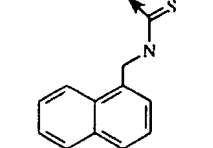
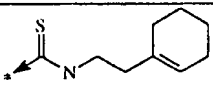
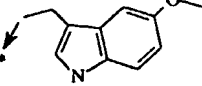
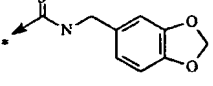
369	"		"	88,55	4,6	415,2
370	"		"	95,93	4,9	365,3
371	"		"	99,1	2,6	360,2
372			"	90,59	3,4	392,1
373	"		"	93,57	3,3	392,2
374	"		"	97,23	2,6	414,2
375	"		"	93,83	3,1	352,3
376	"		"	96,81	4,0	452,4
377	"		"	97,7	2,2	383,3
378	"		"	53,69	2,3	362,2
379	"		"	97,1	3,1	402,1

380	"		"	70,3	2,5	345,3
381	"		"	97,59	3,1	380,2
382	"		"	86,74	2,4	314,2
383	"		"	87,28	2,6	304,3
384	"		"	10,27	3,1	400,2
385	"		"	93,38	3,1	394,2
386	"		"	88,99	3,4	344,3
387	"		"	89,43	2,5	339,3
388			H → "	86,18	4,2	458,3
389	"		"	37,01	3,9	404,3
390	"		"	57,02	2,7	437,4
391	"		"	78,70	4,3	441,3
392	"		"	67,94	4,6	490,3

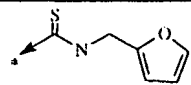
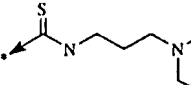
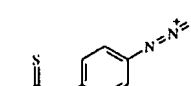
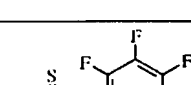
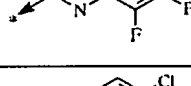
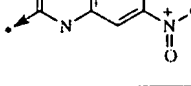
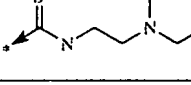
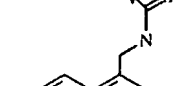
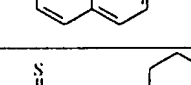
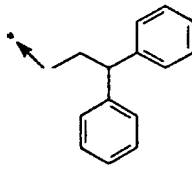
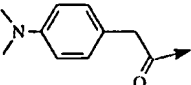
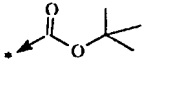
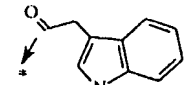
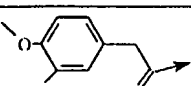
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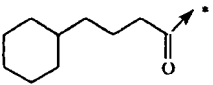
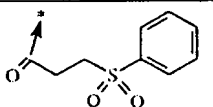
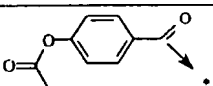
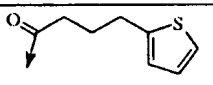
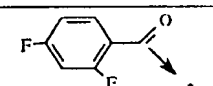
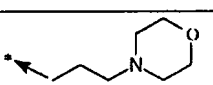
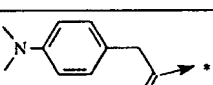
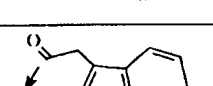
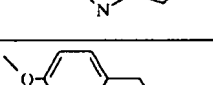
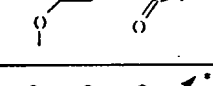

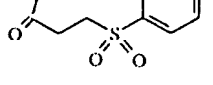
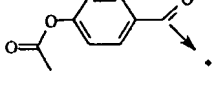
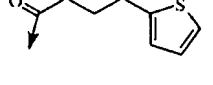
393	"		"	39,75	4,5	479,3
394	"		"	94,48	2,8	435,4
395	"		"	83,7	3,4	432,3
396	"		"	96,5	4,7	464,4
397	"		"	43,75	4,5	547,3
398			"	86,87	3,3	399,3
399	"		"	47,77	2,9	345,3
400	"		"	82	3,4	382,3
401	"		"	97,10	3,8	431,2
402	"		"	76,92	3,8	420,2
403	"		"	97,3	2,8	373,3
404	"		"	95,9	4,0	405,3

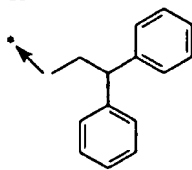
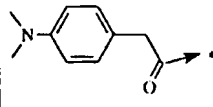

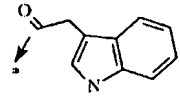
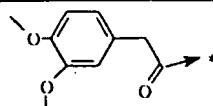
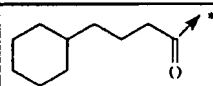
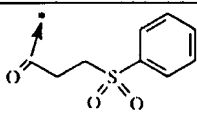
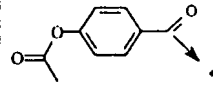
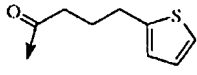
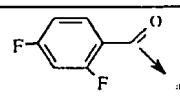
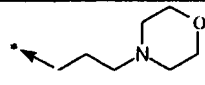
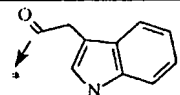
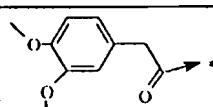
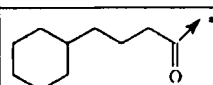
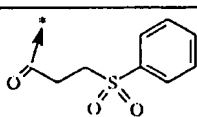
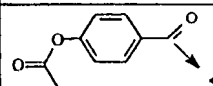
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405	"		"	69,50	3,7	488,3
406			"	90,79	4,1	420,3
407	"		"	86,38	2,5	399,3
408	"		"	67,52	4,6	452,2
409	"		"	99,8	2,7	397,3
410	"		"	97,7	3,3	394,3
411			"	87,97	5,0	488,3
412	"		"	97,23	3,6	467,4
413	"		"	99,29	3,7	465,4
414	"		"	96,2	4,2	462,4
415	"		"	72,0	5,5	494,3
416			"	85,09	4,3	467,3

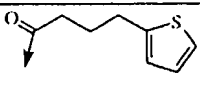
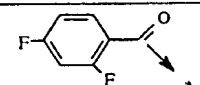
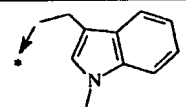
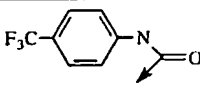
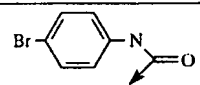
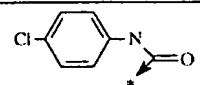
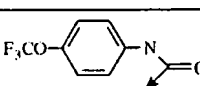
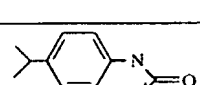
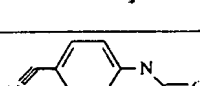
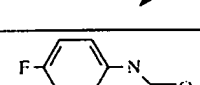
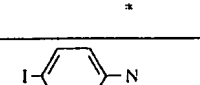
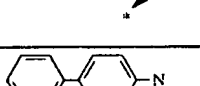
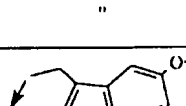

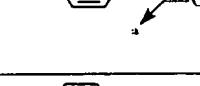
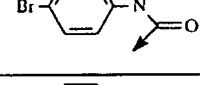
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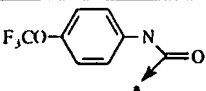
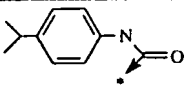
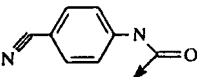
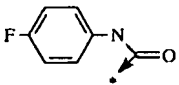
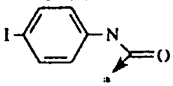
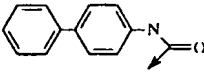
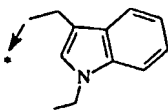
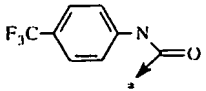
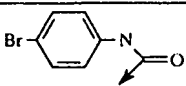
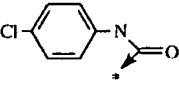
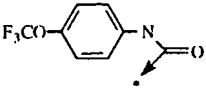
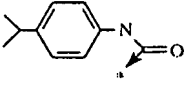
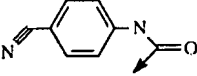
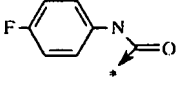
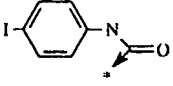
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418	"		"	98,76	2,8	446,4
419	"		"	73,21	4,4	450,3
420	"		"	76,94	4,7	499,2
421	"		"	85,12	4,6	488,2
422	"		"	98,15	2,9	444,4
423	"		"	58	5,1	477,3
424	"		"	25	3,6	410,3
425	"		"	69,90	4,6	556,3
426				90,11	8,2	556,3
427	"		"	95,30	9,7	552,3
428	"		"	89,35	9,6	573,3

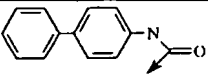
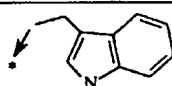
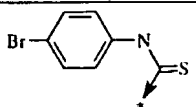
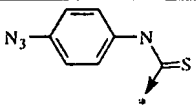
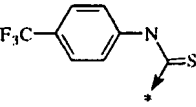
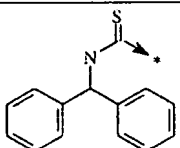
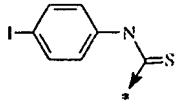
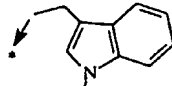
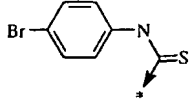
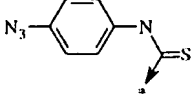
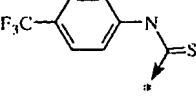
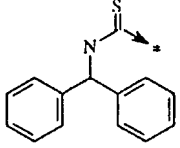
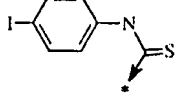
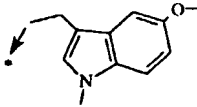
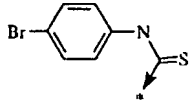
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430	"		"	91,35	9,6	591,3
431	"		"	66,60	9,7	557,3
432	"		"	97,25	10,5	547,3
433	"		"	98,20	10,2	549,3
434			"	88,28	4,7	489,3
435	"		"	94,30	5,8	485,3
436	"		"	92,92	5,6	506,3
437	"		"	95,73	7,1	480,4
438	"		"	89,80	5,6	524,3
439	"		"	69,38	5,6	490,3
440	"		"	95,21	6,2	480,3
441	"		"	96,98	6,0	482,3

442				85,00	5,4	456,3
443	"		"	94,40	6,5	452,3
444	"		"	91,10	6,3	473,3
445	"		"	96,60	7,7	447,3
446	"		"	92,80	6,3	491,2
447	"		"	85,40	6,3	457,2
448	"		"	96,70	6,9	447,2
449	"		"	98	6,7	449,2
450			"	38,17	3,6	385,2
451	"		"	92,70	3,4	406,2
452	"		"	89,50	4,7	380,3
453	"		"	86,24	3,4	424,2
454	"		"	71,20	3,3	390,2

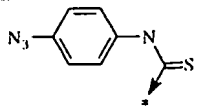
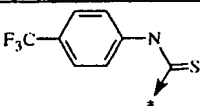
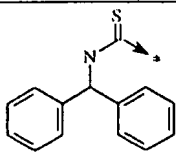
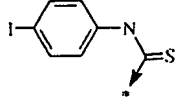
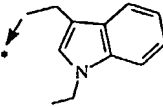
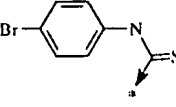
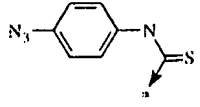
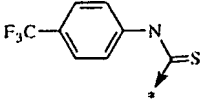
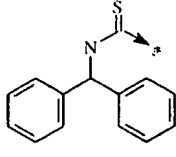
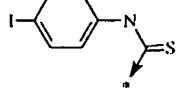
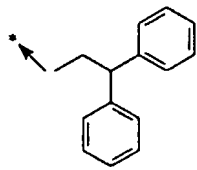
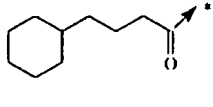
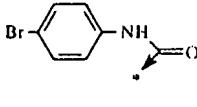
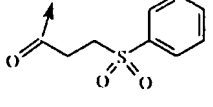
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455	"		"	88,60	3,8	380,2
456	"		"	89,26	3,5	382,2
457			"	96,55	4,9	445,3
458	"		"	94,46	4,8	455,2
459	"		"	95,6	4,7	411,3
460	"		"	98,1	5,0	461,3
461	"		"	93,31	5,1	419,4
462	"		"	97,08	4,2	402,3
463	"		"	94,61	4,4	395,3
464	"		"	97,05	4,9	503,2
465	"		"	95,13	5,1	453,4
466			"	93,21	4,8	475,3
467	"		"	94,08	4,7	485,2
468	"		"	93,08	4,6	441,3

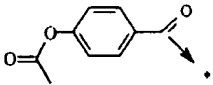
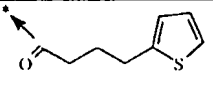
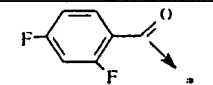
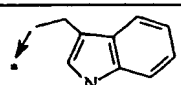
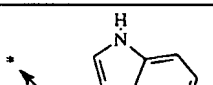
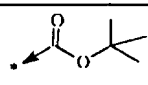

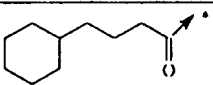
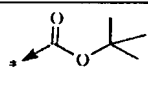

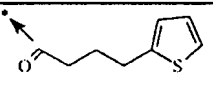
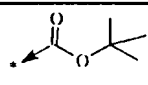

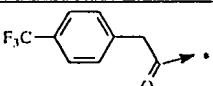
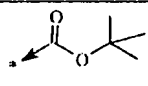

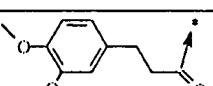
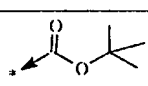

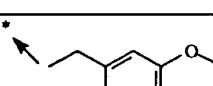
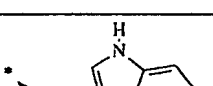
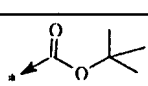

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470	"		"	89,99	5,0	449,4
471	"		"	92	4,1	432,3
472	"		"	94,71	4,3	425,3
473	"		"	95,3	4,8	533,2
474	"		"	94,13	5,0	483,4
475			"	95	5,1	459,3
476	"		"	94,69	5,0	469,2
477	"		"	94,44	4,9	425,3
478	"		"	98	5,2	475,3
479	"		"	96,2	5,3	433,4
480	"		"	93	4,4	416,3
481	"		"	94,59	4,6	409,3
482	"		"	95,22	5,1	517,2

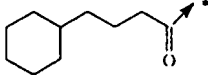
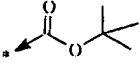

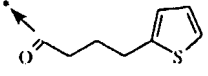
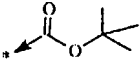

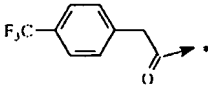
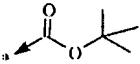

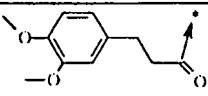
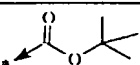

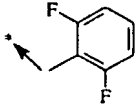
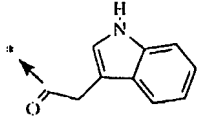
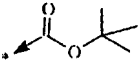

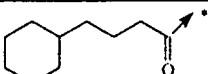
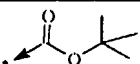

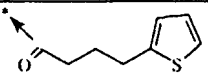
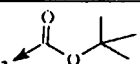

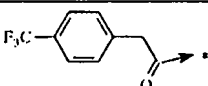
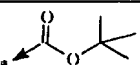
483	"		"	95,7	5,3	467,4
484			"	94,8	4,6	457,2
485	"		"	86,7	4,5	420,3
486	"		"	88,5	4,8	447,3
487	"		"	96,9	5,1	483,4
488	"		"	92,3	4,7	505,2
489			"	65,4	4,9	471,2
490	"		"	62,6	4,7	434,3
491	"		"	57,9	5,0	461,3
492	"		"	94,2	5,3	497,4
493	"		"	54,0	5,0	519,2
494			"	54,6	4,8	501,3

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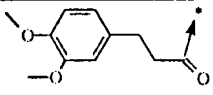
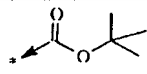

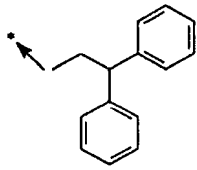
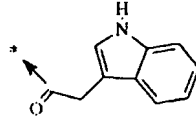
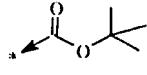

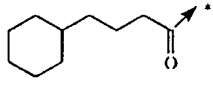
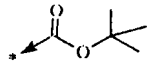

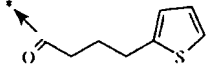
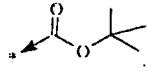

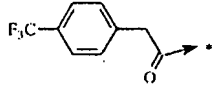
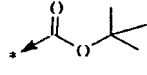

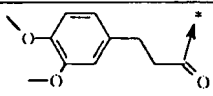
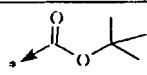

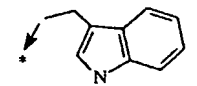
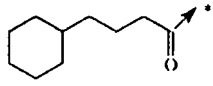
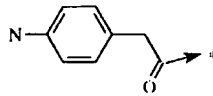
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496	"		"	70,4	4,9	491,3
497	"		"	96,5	5,2	527,4
498	"		"	55,7	4,9	549,2
499			"	57,4	5,1	485,3
500	"		"	59,3	4,9	448,4
501	"		"	53,6	5,2	475,3
502	"		"	97,8	5,4	511,4
503	"		"	10 +36,87	5,2	533,2
504				96,33	11,2	646,3
505	"		"	92,67	9,4	690,1

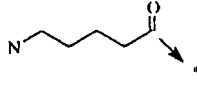
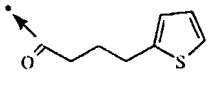
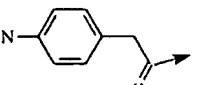
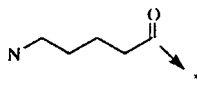
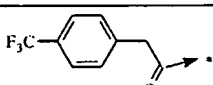
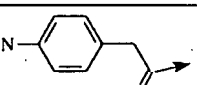
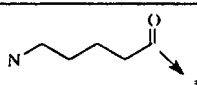
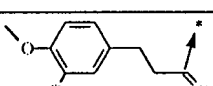
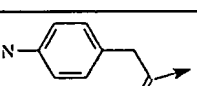
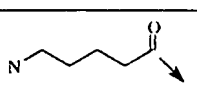
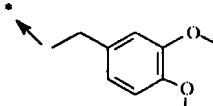
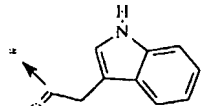
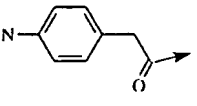
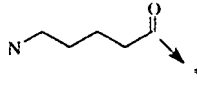
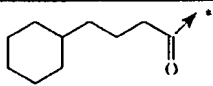
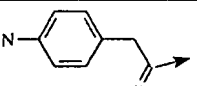
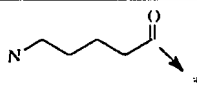
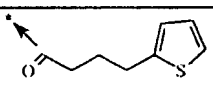
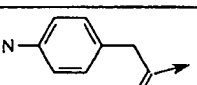
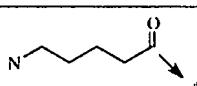
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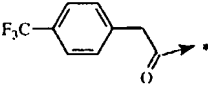
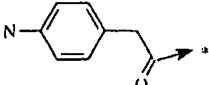
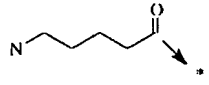
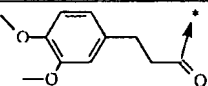
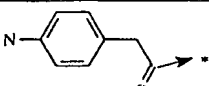
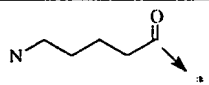
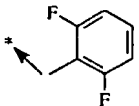
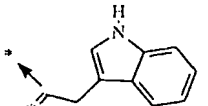
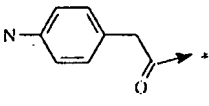
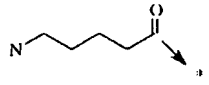
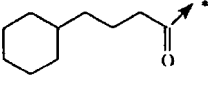
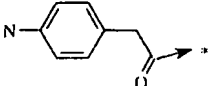
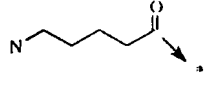
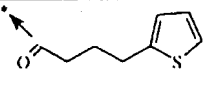
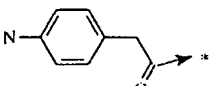
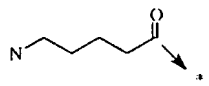
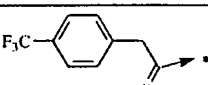
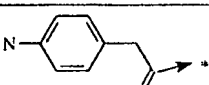
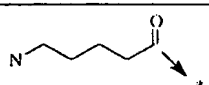
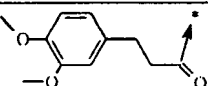
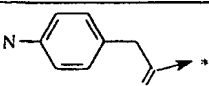
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507	"		"	97.65	10.1	646,2
508	"		"	96.29	9.9	648,2
509				90.89	8.5	501,3
510	"	"	H 	61.04	5.8	401,2
511	"			99.16	10.5	496,4
512	"	"	H 	95.73	7.1	396,3
513	"			66	9.3	496,3
514	"	"	H 	95.00	8.9	396,2
515	"			96.61	9.5	530,3
516	"	"	H 	94.05	6.4	430,3
517	"			87	8.6	536,3
518	"	"	H 	91.59	5.6	436,3
519				86,84	8,4	522,3
520	"	"	H 	94.18	5.4	422,3

521	"			99.75	10.4	517.4
522	"	"	H 	96.8	6.8	417.4
523	"			70.34	9.1	517.3
524	"	"	H 	93.49	5.8	417.3
525	"			93.03	9.3	551.3
526	"	"	H 	97.13	6.1	451.3
527	"			74.37	8.4	557.3
528	"	"	H 	92.92	5.3	457.3
529				92.92	8.8	484.3
530	"	"	H 	92.68	5.5	384.2
531	"			98.29	10.8	479.3
532	"	"	H 	96.39	7.0	379.3
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534	"	"	H 	99.76	6.0	379.2
535	"			99.17	9.7	513.2

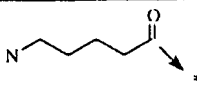
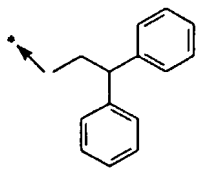
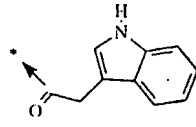
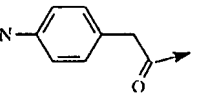
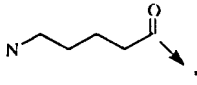
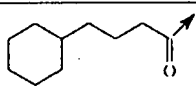
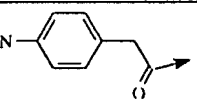
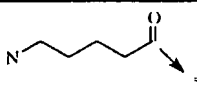
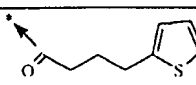
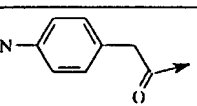
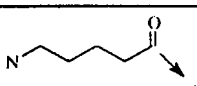
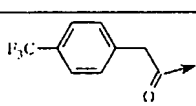
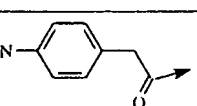
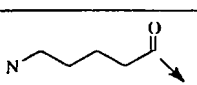
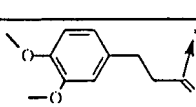
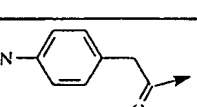
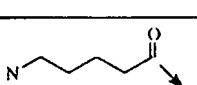
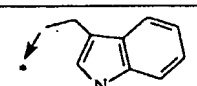
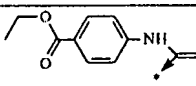
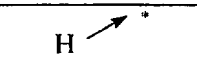
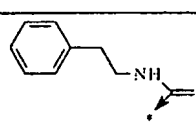
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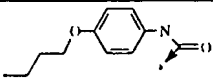
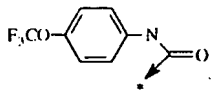
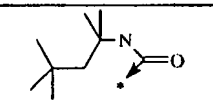
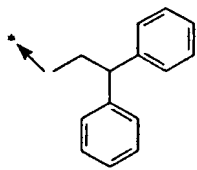
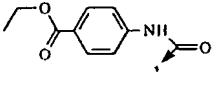
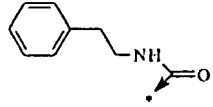
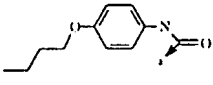
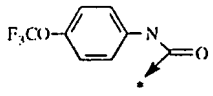
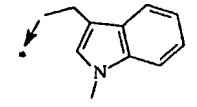
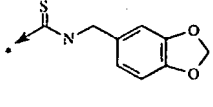
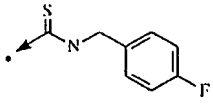
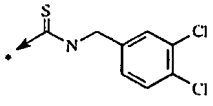
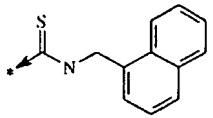
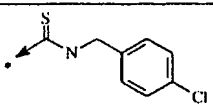
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539				91,37	9,8	552,3
540	"	"		95,39	6,6	452,3
541	"			98,71	11,7	547,4
542	"	"		99,02	7,9	447,4
543	"			79,38	10,5	547,3
544	"	"		95,46	7,1	447,3
545	"			95,3	10,6	581,3
546	"	"		95,45	7,3	481,3
547	"			80,92	9,8	587,3
548	"	"		92,06	6,5	487,3
549				63	7,7	529,4

550	"	"		79	7.1	495.4
551	"			70	6.7	529.3
552	"	"		77	6.3	495.3
553	"			61	6.9	563.3
554	"	"		69	6.5	529.3
555	"			69	6.1	569.3
556	"	"		76	5.8	535.3
557				79	5.9	555.3
558	"	"		88	5.6	521.3
559	"			90.81	7.4	550.4
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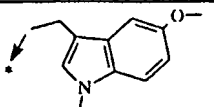
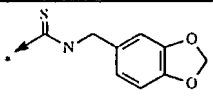
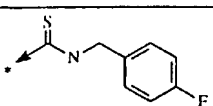
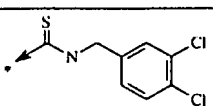
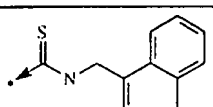
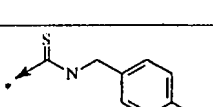
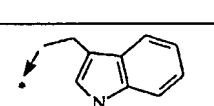
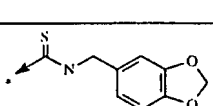
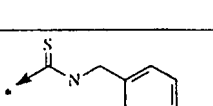
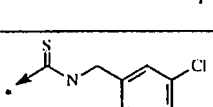
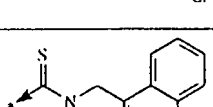
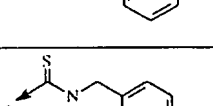

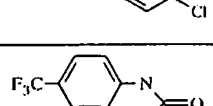
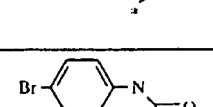
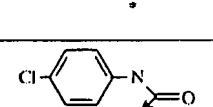
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565	"			82.91	5.8	590,3
566	"	"		87.77	5.5	556,3
567				86	6.0	517,3
568	"	"		83.41	5.7	483,3
569	"			95	7.6	512,3
570	"	"		94.08	7.1	478,4
571	"			87.39	6.5	512,3
572	"	"		90.06	6.1	478,3
573	"			85.61	6.8	546,2
574	"	"		83.51	6.4	512,3
575	"			78.63	5.9	552,3

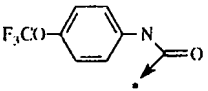
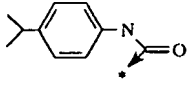
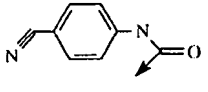
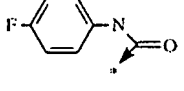
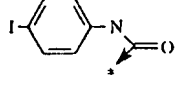
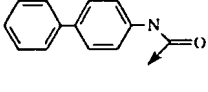
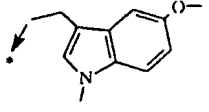
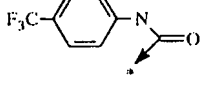
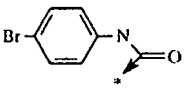
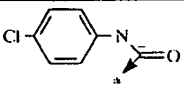
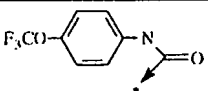
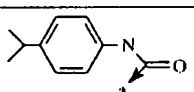
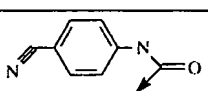
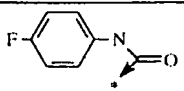
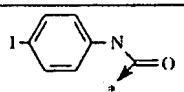
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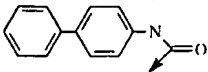
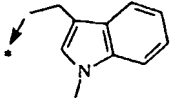
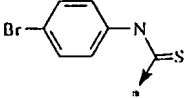
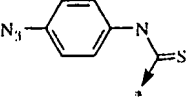
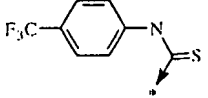
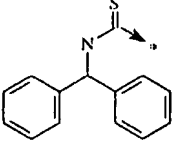
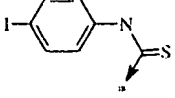
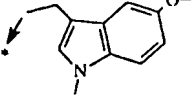
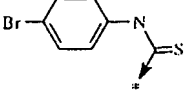
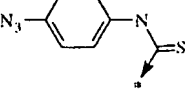
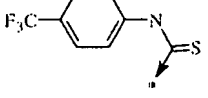
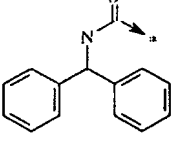
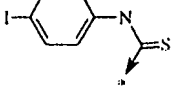
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577				84	7,1	585,3
578	"	"		91	6,7	551,3
579	"			89,59	8,6	580,4
580	"	"		97,13	7,9	546,4
581	"			83	7,6	580,3
582	"	"		92,05	7,1	546,3
583	"			86	7,8	614,3
584	"	"		95,49	7,3	580,3
585	"			77	7,0	620,3
586	"	"		91,1	6,6	586,4
587				95	4,6	435
588	"		"	90	4,4	391,3

589	"		"	88	5.1	435.3
590	"		"	92	4.9	447.3
591	"		"	20.32	5.1	399.4
592			"	85	5.3	486.3
593	"		"	97	5.1	442.3
594	"		"	92	5.7	486.4
595	"		"	79	5.5	498.3
596			"	93.4	4.68	451.29
597	"		"	94.9	4.86	425.27
598	"		"	97.9	5.37	475.22
599	"		"	97.1	5.20	457.32
600	"		"	95.1	5.10	441.24

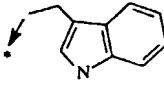
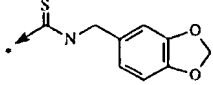
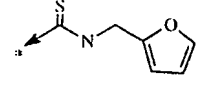
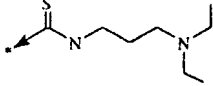
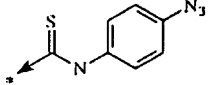
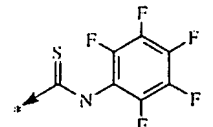
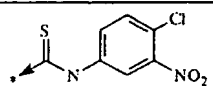
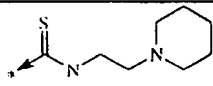
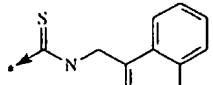
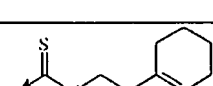
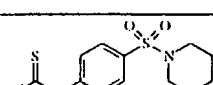
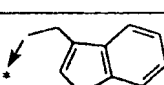
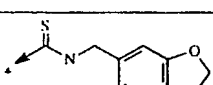
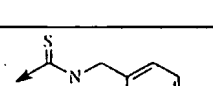
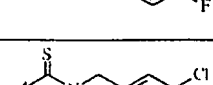
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601			"	91.1	4.61	481.29
602	"		"	97.5	4.78	455.29
603	"		"	98.0	5.28	505.22
604	"		"	95.4	5.12	487.33
605	"		"	94.0	5.03	471.27
606			"	89.8	4.86	465.29
607	"		"	98.2	5.03	439.29
608	"		"	97.6	5.53	489.24
609	"		"	93.3	5.36	471.34
610	"		"	91.4	5.27	455.26
611			$\text{CH}_3 \rightarrow$	94	4.9	459.3
612	"		"	92.95	4.8	469.2
613	"		"	91.61	4.7	425.3

614	"		"	92	5,0	475,3
615	"		"	85,2	5,1	433,4
616	"		"	83	4,2	416,3
617	"		"	94,11	4,4	409,3
618	"		"	93,85	5,0	517,2
619	"		"	92,74	5,1	467,4
620			"	91	4,8	489,3
621	"		"	91,9	4,7	499,3
622	"		"	89,71	4,6	455,3
623	"		"	90	4,9	505,3
624	"		"	83,96	5,0	463,4
625	"		"	87	4,1	446,3
626	"		"	93,1	4,3	439,3
627	"		"	93,21	4,8	547,2

628	"		"	90,67	5,0	497,4
629			"	79,6	4,9	485,2
630	"		"	72,8	4,8	448,3
631	"		"	78,7	5,1	475,3
632	"		"	97,3	5,4	511,4
633	"		"	51,5	5,1	533,2
634			"	76,1	4,9	515,3
635	"		"	74,2	4,7	478,3
636	"		"	76,5	5,0	505,3
637	"		"	97,7	5,3	541,4
638	"		"	71,4	5,0	563,2

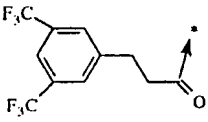
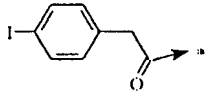
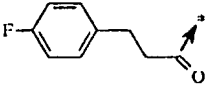
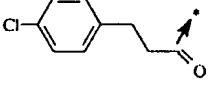
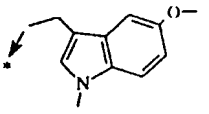
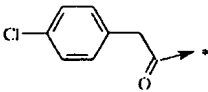
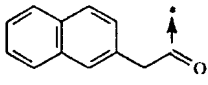
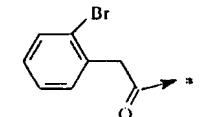
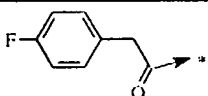
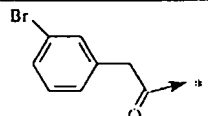
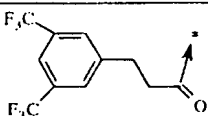
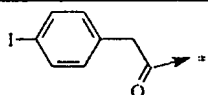
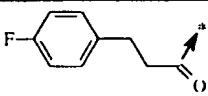
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639			"	82,54	4,4	451,3
640	"		"	93,42	4,2	397,3
641	"		"	98,93	2,9	430,4
642	"		"	81,46	4,5	434,3
643	"		"	96,41	4,9	483,3
644	"		"	91,55	4,7	472,3
645	"		"	97,96	2,9	428,4
646	"		"	96,9	5,0	425,3
647	"		"	95,8	4,9	457,3
648	"		"	91,41	4,6	540,3
649			"	88,0	4,75	465,3
650	"		"	99,0	4,89	439,3
651	"		"	98,5	5,42	489,2

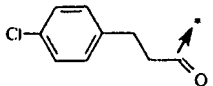
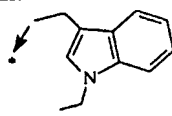
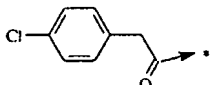
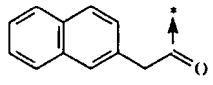
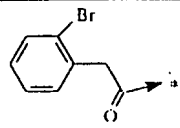
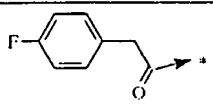
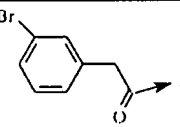
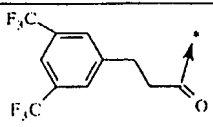
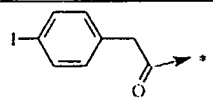
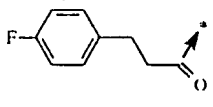
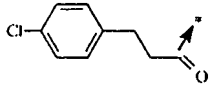
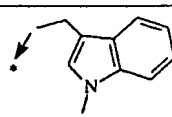
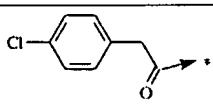
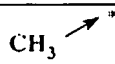
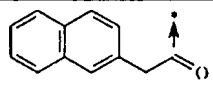
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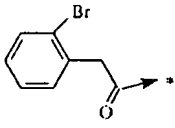
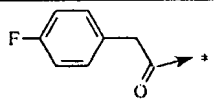
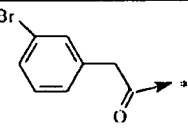
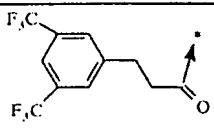
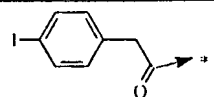
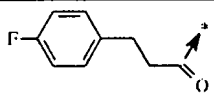
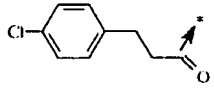
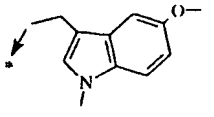
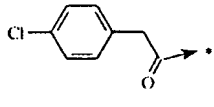
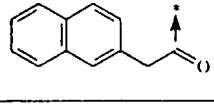
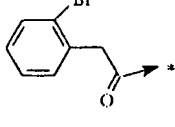
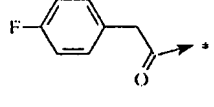
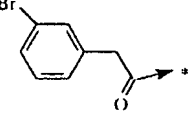
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653	"		"	87.6	5.14	455.3
654			"	88.3	4.66	495.3
655	"		"	98.1	4.82	469.3
656	"		"	98.4	5.34	519.2
657	"		"	95.4	5.16	501.3
658	"		"	89.8	5.08	485.3
659			H → *	80.76	4.84	410.2
660	"		"	61.69	4.97	426.2
661	"		"	90.93	4.79	454.1
662	"		"	91.55	4.58	394.2
663	"		"	91.99	4.88	454.1

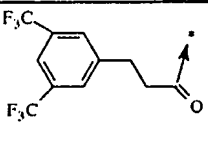
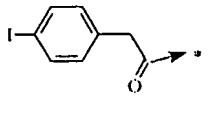
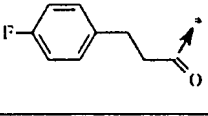
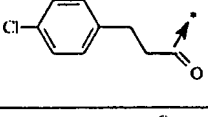
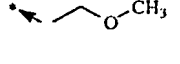
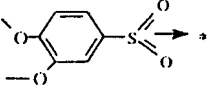

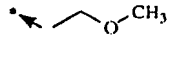
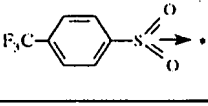
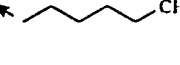
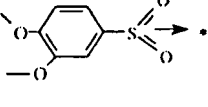
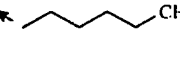
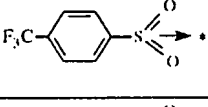
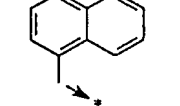
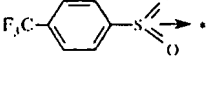
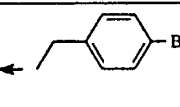
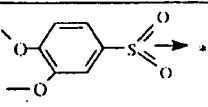
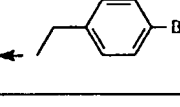
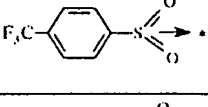
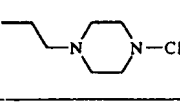
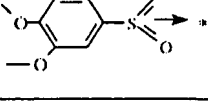
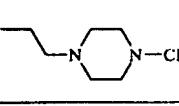
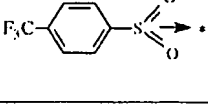
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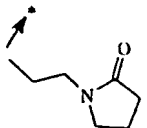
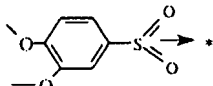
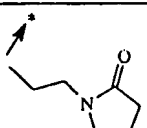
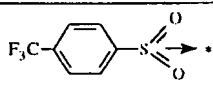
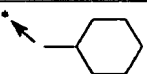
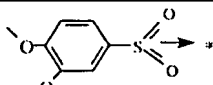
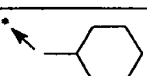
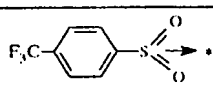
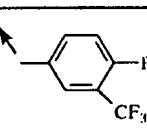
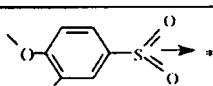
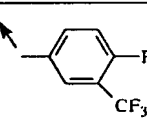
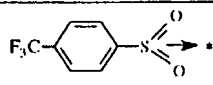
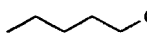
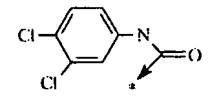
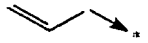
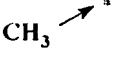
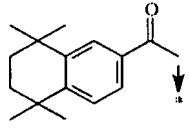
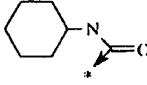
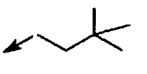
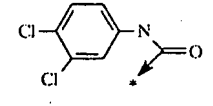
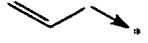
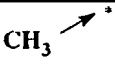
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665	"		"	93,78	5,02	502,1
666	"		"	96,3	4,75	408,2
667	"		"	81,2	5,02	408,2
668			"	90,79	4,74	440,2
669	"		"	78,93	4,88	456,3
670	"		"	91,87	4,69	484,2
671	"		"	91,19	4,51	424,2
672	"		"	95,27	4,79	484,2
673	"		"	89,5	5,46	542,2
674	"		"	90,77	4,92	532,1
675	"		"	95,1	4,66	438,2

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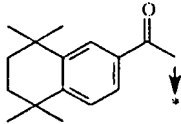
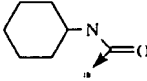
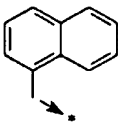
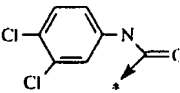
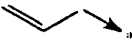
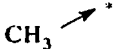
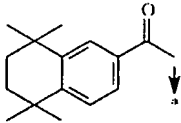
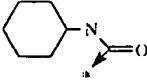
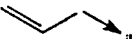
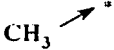
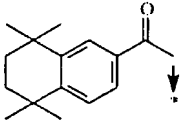
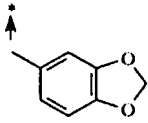
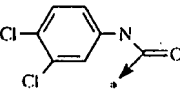
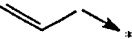
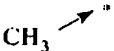
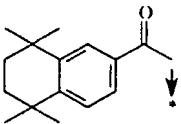
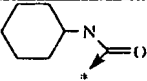
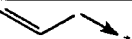
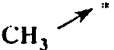
676	"		"	88,7	4,92	524,2
677			"	81,65	4,99	424,2
678	"		"	70,32	5,11	440,3
679	"		"	90,06	4,96	468,2
680	"		"	94,11	4,74	408,2
681	"		"	93,96	5,04	468,2
682	"		"	93,3	5,66	540,2
683	"		"	94,79	5,16	516,1
684	"		"	96,5	4,9	422,3
685	"		"	88,2	5,19	438,2
686				87,93	4,86	424,2
687	"		"	84,74	5	440,2

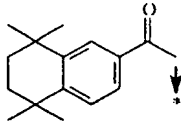
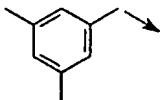
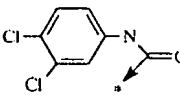
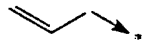

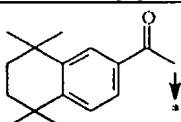
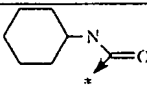
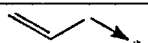

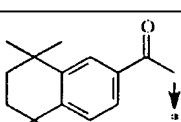
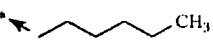
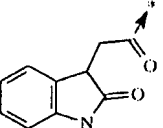
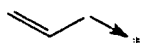

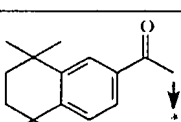
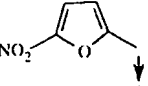
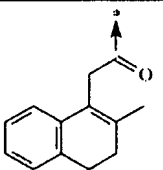
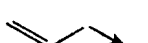
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689	"		"	89,78	4,6	408,2
690	"		"	95,16	4,9	468,163 3
691	"		"	95,6	5,56	540,2
692	"		"	95,24	5,05	516,3
693	"		"	96,6	4,8	422,2
694	"		"	90,4	5,04	438,2
695			"	93,12	4,78	454,2
696	"		"	86,11	4,92	470,3
697	"		"	94,89	4,73	498,2
698	"		"	94,1	4,54	438,3
699	"		"	95,66	4,81	498,2

700	"		"	94.8	5.48	570.2
701	"		"	93.63	4.96	546.1
702	"		"	96.7	4.7	452.3
703	"		"	85.6	4.96	468.2
704			H 	78.36	3.14	359.1
705			"	47.4	3.9	367.1
706			"	69.72	4.28	385.2
707			"	34.86	4.96	393.2
708			"	37.54	4.91	449.2
709			"	81.57	4.46	483.1
710			"	55.98	5.12	491.1
711			"	73.74	3.09	441.2
712			"	40.19	2.85	449.2

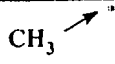
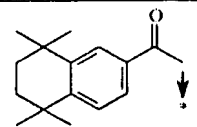
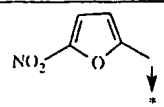
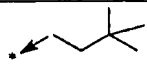
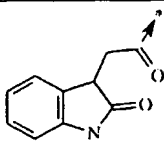
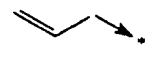
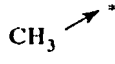
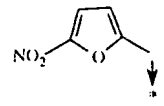
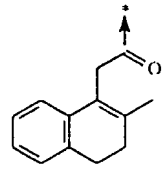
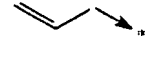
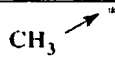
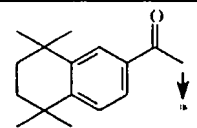
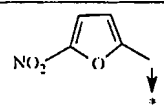
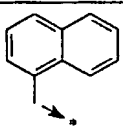
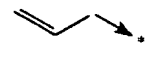
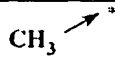
713			"	90,07	3,18	426,2
714			"	74,98	3,84	434,2
715			"	78,14	4,24	397,2
716			"	39,87	4,92	405,2
717			"	57,34	4,45	477,2
718			"	37,75	5,01	485,1
719				70,3	5,2	412,1
720	"	"		70,7	5,0	386,1
721	"	"		61,9	6,3	600,3
722	"		"	49,3	6,1	538,4
723				65,0	5,1	412,2
724	"	"		44,3	4,9	386,2

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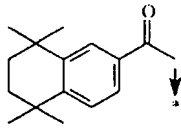
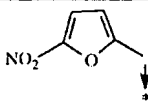
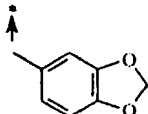
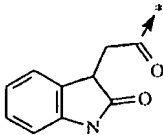
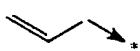
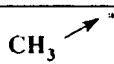
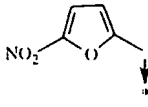
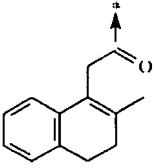
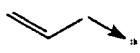
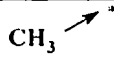
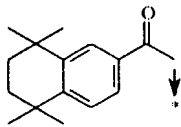
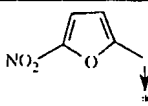
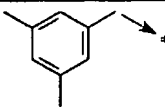
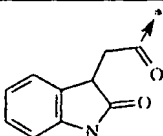
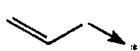
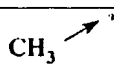
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726	"		"	37,5	6,0	538,4
727				87,1	5,1	468,1
728	"	"	CH_3 	84,4	4,9	442,1
729	"	"		82,3	6,2	656,3
730	"			93,8	4,7	406,3
731	"	"	CH_3 	80,7	4,6	380,3
732	"	"		84,1	5,9	594,3
733				67,9	4,7	462,1
734	"	"	CH_3 	66,9	4,6	436,1
735	"	"		56,8	5,9	650,2
736	"			88,1	4,3	400,3
737	"	"	CH_3 	82,8	4,1	374,3

738	"	"		51.4	5.6	588,3
739				77.7	5.1	446,2
740	"	"	CH_3 	76.1	4.9	420,2
741	"	"		67.1	6.2	634,3
742	"			88.9	4.7	384,3
743	"	"	CH_3 	79.3	4.5	358,3
744	"	"		65.1	5.9	572.4
745				80,0	4,0	398,3
746	"	"	CH_3 	76.9	3.8	372,3
747	"	"		42.7	5.8	586,4
748	"	"		64.6	4.4	483,3
749	"			87.4	5.3	409,3

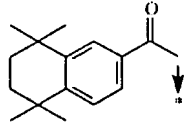
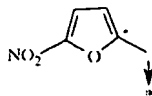
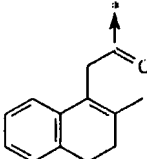
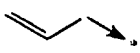
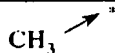
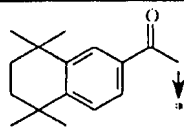
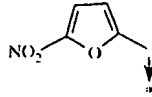
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750	"	"		71.0	5.1	383.3
751	"	"		59.8	6.7	597.4
752	"	"		84.4	5.6	494.3
753				80.1	3.9	398.3
754	"	"		63.1	3.7	372.3
755	"	"		64.4	4.3	483.3
756	"			84.6	5.3	409.3
757	"	"		59.6	5.0	383.3
758	"	"		52.9	6.6	597.4
759	"	"		81.6	5.5	494.3
760		"		75.3	5.3	465.3
761	"	"		60.3	5.1	439.3

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762	"	"		61.8	6.6	653,4
763	"	"		74,4	5,6	550,3
764				74,5	3,6	448,2
765	"	"	CH_3 	51.3	3.4	422,2
766	"	"		58.8	3,9	533,2
767	"			86.2	4,8	459,3
768	"	"	CH_3 	63.2	4,6	433,3
769	"	"		60.1	6,2	647,4
770	"	"		83,5	5,1	544,2
771				68.1	4,1	432,3
772	"	"	CH_3 	63,8	3,9	406,2

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773	"	"		41.1	5.8	620,4
774	"	"		62.8	4.4	517.2
775	"			85.5	5.4	443,3
776	"	"		62.5	5.2	417,3
777	"	"		66.0	6.7	631,4
778	"	"		87.7	5.6	528.3

Etude pharmacologique

Les composés de la présente invention ont été testés en ce qui concerne leur affinité pour différents sous-types de récepteurs de la somatostatine selon les procédures décrites ci-après.

5 *Etude de l'affinité pour les sous-types de récepteurs de la somatostatine humaine :*

L'affinité d'un composé de l'invention pour les sous-types de récepteurs de la somatostatine 1 à 5 (sst₁, sst₂, sst₃, sst₄ et sst₅, respectivement) est déterminée par la mesure de l'inhibition de la liaison de [¹²⁵I-Tyr¹¹]SRIF-14 à des cellules transfectées CHO-K1.

- 10 Le gène du récepteur sst₁ de la somatostatine humaine a été cloné sous forme d'un fragment génomique. Un segment *Pst*I-*Xmn*I de 1,5 Kb contenant 100 pb de la région 5' non transcrite, 1,17 Kb de la région codante en totalité, et 230 bp de la région 3' non transcrite est modifié par l'addition du linker *Bgl*II. Le fragment d'ADN résultant est souscloné dans le site *Bam*HI d'un pCMV-81 pour donner le
- 15 plasmide d'expression chez les mammifères (fourni par Dr. Graeme Bell, Univ. Chicago). Une lignée de cellules clonées exprimant de façon stable le récepteur sst₁ est obtenue par transfection dans des cellules CHO-K1 (ATCC) grâce à la méthode de co-précipitation calcium phosphate. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées de cellules clonées ont été sélectionnées
- 20 dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Le gène du récepteur sst₂ de la somatostatine humaine, isolé sous forme d'un fragment génomique d'ADN de 1,7 Kb *Bam*HI-*Hind*III et souscloné dans un vecteur plasmidique pGEM3Z (Promega), a été fourni par le Dr. G. Bell (Univ. of Chicago).

- 25 Le vecteur d'expression des cellules de mammifères est construit en insérant le fragment *Bam*HI-*Hind*III de 1,7 Kb dans des sites de restriction endonucléase compatibles du plasmide pCMV5. Une lignée de cellules clonées est obtenue par transfection dans des cellules CHO-K1 grâce à la méthode de co-précipitation calcium phosphate. Le plasmide pRSV-neo est inclus comme marqueur de sélection.

- 30 Le récepteur sst₃ est isolé comme fragment génomique, et la séquence codante complète est contenue dans un fragment *Bam*HI/*Hind*III de 2,4 Kb. Le plasmide d'expression chez les mammifères, pCMV-h3, est construit par insertion du fragment *Nco*I-*Hind*III de 2,0 Kb dans le site *Eco*R1 du vecteur pCMV après modification des

terminaisons et addition de linkers EcoR1. Une lignée de cellules clonées exprimant de façon stable le récepteur sst₃ est obtenue par transfection dans des cellules CHO-K1 (ATCC) par la méthode de co-précipitation au phosphate de calcium. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées
5 de cellules clonées ont été sélectionnées dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Le plasmide d'expression du récepteur sst₄ humain, pCMV-HX, a été fourni par le Dr. Graeme Bell (Univ. Chicago). Ce vecteur contient le fragment génomique codant pour le récepteur sst₄ humain de 1,4 Kb *NheI-NheI*, 456 pb de la région 5' non
10 transcrite, et 200 pb de la région 3' non transcrite, cloné dans les sites *XbaI/EcoR1* de pCMV-HX. Une lignée de cellules clonées exprimant de façon stable le récepteur sst₄ est obtenue par transfection dans des cellules CHO-K1 (ATCC) par la méthode de co-précipitation au phosphate de calcium. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées de cellules clonées ont été
15 sélectionnées dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Le gène correspondant au récepteur sst₅ humain, obtenu par la méthode PCR en utilisant un clone génomique λ comme sonde, a été fourni par le Dr. Graeme Bell (Univ. Chicago). Le fragment PCR résultant de 1,2 Kb contient 21 paires de bases de
20 la région 5' non transcrites, la région codante en totalité, et 55 pb de la région 3' non transcrite. Le clone est inséré dans un site EcoR1 du plasmide pBSSK(+). L'insert est récupéré sous la forme d'un fragment *HindIII-XbaI* de 1,2 Kb pour sous-clonage dans un vecteur d'expression chez les mammifères, pCVM5. Une lignée de cellules clonées exprimant de façon stable le récepteur sst₅ est obtenue par transfection dans
25 des cellules CHO-K1 (ATCC) par la méthode de co-précipitation au phosphate de calcium. Le plasmide pRSV-neo (ATCC) est inclus comme marqueur de sélection. Des lignées de cellules clonées ont été sélectionnées dans un milieu RPMI 1640 contenant 0,5 mg/ml de G418 (Gibco), clonées en cercle, et multipliées en culture.

Les cellules CHO-K1 exprimant de façon stable l'un des récepteurs sst humain sont
30 cultivées dans un milieu RPMI 1640 contenant 10 % de sérum foetal de veau et 0,4 mg/ml de généticine. Les cellules sont collectées avec de l'EDTA 0,5 mM et centrifugées à 500 g pendant environ 5 min à environ 4° C. Le centrifugat est re-suspendu dans un milieu tampon 50 mM Tris à pH 7,4 et centrifugé deux fois à 500 g pendant environ 5 min à environ 4° C. Les cellules sont lysées par sonication
35 et centrifugées à 39 000 g pendant environ 10 min à 4° C. Le centrifugat est

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re-suspendu dans le même milieu tampon et centrifugé à 50 000 g pendant 10 min à environ 4° C et les membranes dans le centrifugat obtenu sont stockées à -80° C.

Des tests d'inhibition compétitive de liaison avec [125 I-Tyr 11]SRIF-14 sont effectués en double à l'aide de plaques en polypropylène de 96 puits. Les membranes
5 cellulaires (10 µg protéine/puits) sont incubées avec [125 I-Tyr 11]SRIF-14 (0,05 nM) pendant environ 60 min à environ 37° C dans un milieu tampon 50 mM HEPES (pH 7,4) comprenant 0,2 % BSA, 5 mM de MgCl $_2$, 200 KIU/ml de Trasylol, 0,02 mg/ml de bacitracine et 0,02 mg/ml de fluorure de phénylméthylsulphonyle.

La [125 I-Tyr 11]SRIF-14 liée est séparée de la [125 I-Tyr 11]SRIF-14 libre par filtration
10 immédiate à travers des plaques filtres en fibre de verre GF/C (Unifilter, Packard) préimprégné avec 0,1 % de polyéthylènimine (P.E.I.), en utilisant un Filtermate 196 (Packard). Les filtres sont lavés avec du tampon 50 mM HEPES à environ 0-4° C pendant environ 4 secondes et leur radioactivité est déterminée à l'aide d'un compteur (Packard Top Count).

15 La liaison spécifique est obtenue en soustrayant la liaison non spécifique (déterminée en présence de 0,1 µM SRIF-14) de la liaison totale. Les données relatives à la liaison sont analysées par analyse en régression non-linéaire assistée par ordinateur (MDL) et les valeurs des constantes d'inhibition (K $_i$) values sont déterminées.

La détermination du caractère agoniste ou antagoniste d'un composé de la présente
20 invention est effectuée à l'aide du test décrit ci-après.

Test fonctionnel : Inhibition de la production d'AMPc intracellulaire :

Des cellules CHO-K1 exprimant les sous-types de récepteurs de la somatostatine humaine (SRIF-14) sont cultivées dans des plaques à 24 puits dans un milieu RPMI
25 1640 avec 10 % de sérum foetal de veau et 0,4 mg/ml de généticine. Le milieu est changé le jour précédant l'expérience.

Les cellules à raison de 10 5 cellules/puits sont lavées 2 fois avec 0,5 ml de nouveau milieu RPMI comprenant 0,2 % BSA complété par 0,5 mM de 3-isobutyl-1-méthylxanthine (IBMX) et incubées pendant environ 5 min à environ 37° C.

. la production d'AMP cyclique est stimulée par l'addition de 1 mM de forskoline
30 (FSK) pendant 15-30 minutes à environ 37° C.

. l'effet inhibiteur de la somatostatine d'un composé agoniste est mesuré par l'addition simultanée de FSK ($1\text{ }\mu\text{M}$) , SRIF-14 (10^{-12} M to 10^{-6} M) et du composé à tester (10^{-10} M à 10^{-5} M).

- 5 . l'effet antagoniste d'un composé est mesuré par l'addition simultanée de FSK ($1\text{ }\mu\text{M}$), SRIF-14 (1 to 10 nM) et du composé à tester (10^{-10} M to 10^{-5} M).

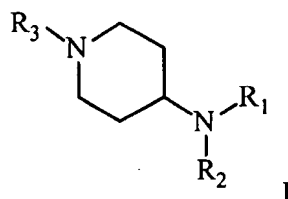
Le milieu réactionnel est éliminé et 200 ml de HCl 0,1 N sont ajoutés. La quantité d'AMPC est mesurée par un test radioimmunologique (Kit FlashPlate SMP001A, New England Nuclear).

Résultats :

- 10 Les tests effectués selon les protocoles décrits ci-dessus ont permis de montrer que les produits de formule générale (I) définie dans la présente demande ont une bonne affinité pour au moins l'un des sous-types de récepteurs de la somatostatine, la constante d'inhibition K_i étant inférieure au micromolaire pour certains des composés exemplifiés.

Revendications

1. Composés de formule générale



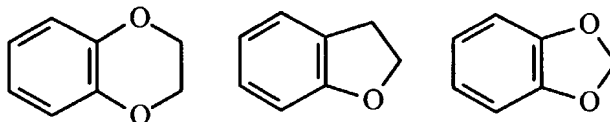
sous forme racémique, d'énantiomère ou toutes combinaisons de ces formes, dans laquelle :

R_1 représente un radical (C_1-C_{16}) alkyle linéaire ou ramifié, alkényle, alkynyle,
 5 $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

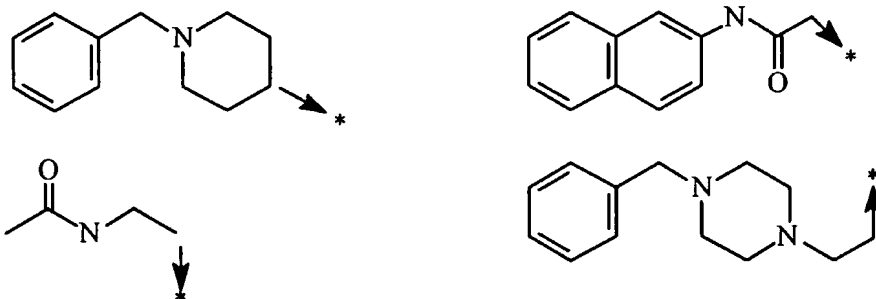
Z_{11} représente un (C_1-C_6) alkyle ou aryle éventuellement substitué,

Z_{12} représente cyano, cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle éventuellement substitué, aryle éventuellement substitué ou hétéroaryle éventuellement substitué,

10 ou bien Z_{12} représente un radical de formule



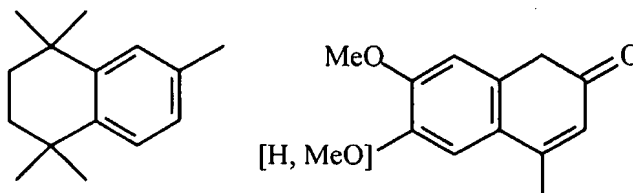
ou bien R_1 représente un radical de formule



R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 ;

R_3 représente l'atome d'hydrogène, un radical alkyle éventuellement substitué, alkényle, alkynyle, aralkyle éventuellement substitué, hétéroarylalkyle
 15 éventuellement substitué, ou un radical de formule $-C(Y)-NHX_1$, $-(CH_2)_n-C(O)X_2$, SO_2X_3 ou

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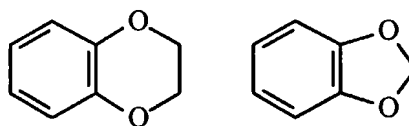


X_1 représente un radical (C_1-C_{15}) alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m-Y-Z_{21}$ ou $-(CH_2)_p-Z_{22}$ dans lequel

Z_{21} représente un (C_1-C_6) alkyle

5 Z_{22} représente cyclohexényle, indanyle, *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou aryle ou hétéroaryle éventuellement substitué,

ou Z_{22} représente un radical de formule

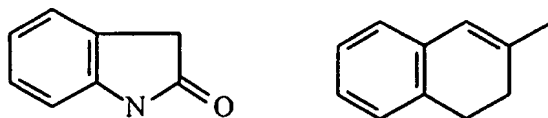
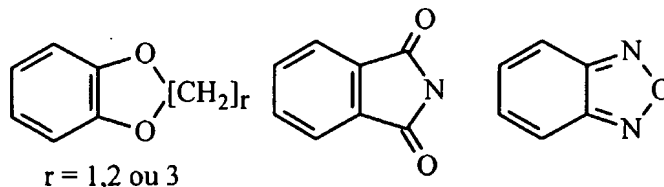


10 X_2 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), alkynyle, ou un radical de formule $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_p-U-Z_{24}$ dans lequel

Z_{23} représente un (C_1-C_6) alkyle ou aryle éventuellement substitué ;

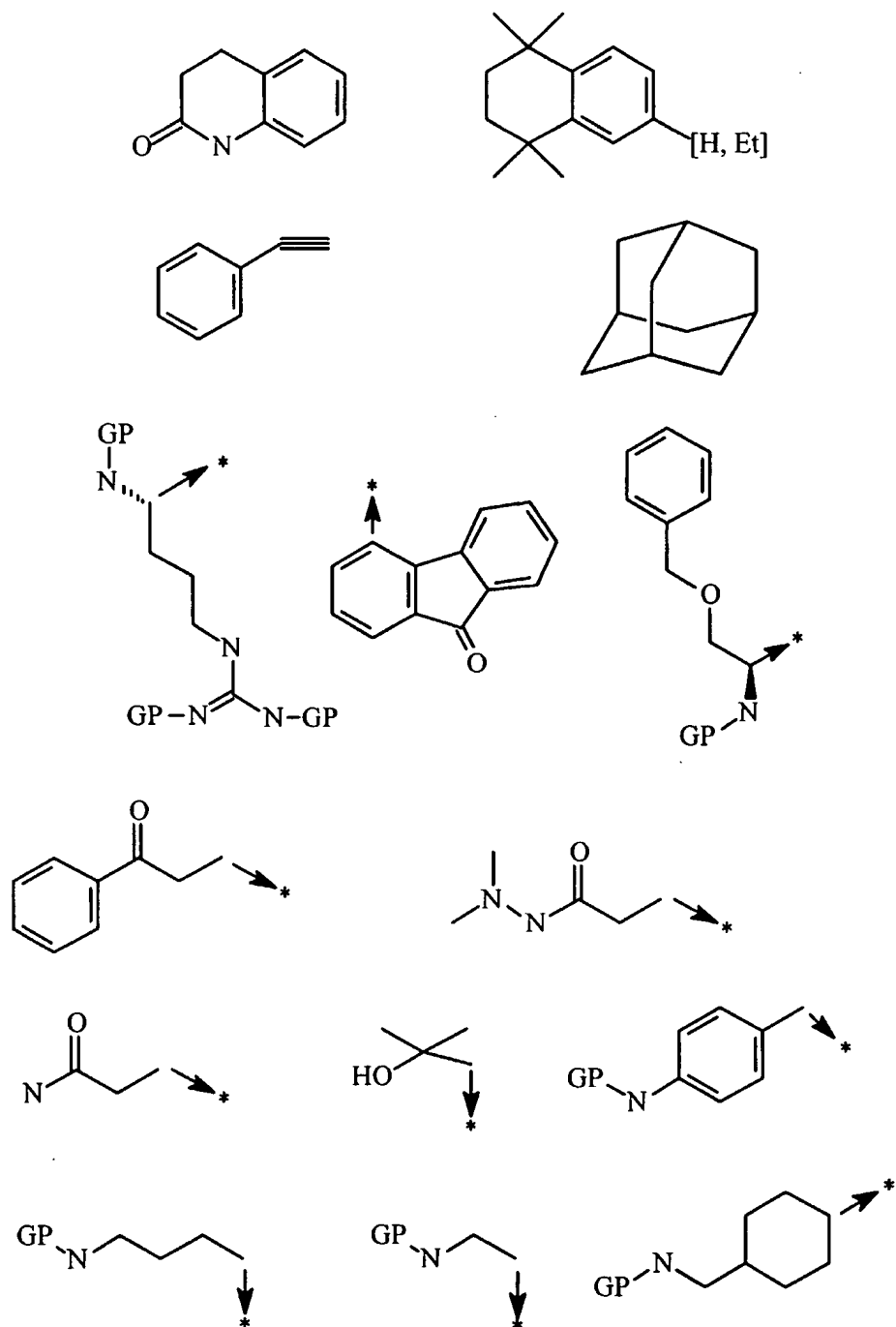
15 Z_{24} représente alkyle, cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle éventuellement substitué, (C_3-C_7) hétérocycloalkyle, cyano, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué,

ou Z_{24} représente un radical de formule



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ou bien X_2 représente un radical représenté ci-dessous :



5

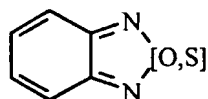
où le groupe protecteur (GP) représente H ou le *tert*-butyloxycarbonyl ;

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X_3 représente un radical (C_1 - C_{10})alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), CF_3 , ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente aryle ou hétéroaryle éventuellement substitué,

5 ou bien X_3 représente un radical de formule



éventuellement substitué par un ou plusieurs radicaux halo

identiques ou différents ;

Y représente un atome d'oxygène ou de soufre ;

W représente un atome d'oxygène, de soufre ou SO_2 ;

U représente une liaison covalente ou l'atome d'oxygène ;

10 n est un entier de 0 à 4 ;

m est un entier de 1 à 6 ;

p est un entier de 0 à 6 ;

q est un entier de 0 à 2,

ou leurs sels d'addition avec les acides minéraux ou organiques pharmaceutiquement
15 acceptables, à l'exclusion des composés de formule générale I dans laquelle R_1 représente le radical alkyle, alkényle ou benzyle, R_2 benzyloxy éventuellement substitué et R_3 aralkyle.

2. Composés de formule générale I telle que définie à la revendication 1, caractérisée en ce que

20 i) le ou les substituant(s) que peuvent porter les radicaux aryle que représentent Z_{11} et Z_{12} et hétéroaryle que représente Z_{12} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, $-CF_3$, $-OCF_3$, phényle, phénoxy, aminosulfonyl ;

ii) le ou les substituant(s) que peut porter le radical hétérocycloalkyle que représente
25 Z_{12} sont choisis indépendamment parmi les radicaux oxy et alkyle ;

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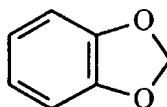
- iii) le ou les substituant(s) que peut porter les radicaux aryle et hétéroaryle que représente Z_{22} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkényle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, aminosulfonyle, pipéridinosulfonyle, mono- ou di-alkylamino, -C(O)-O-alkyle, -C(O)-alkyle, ou phényle, phénoxy, phénylthio, benzyloxy, le radical phényle pouvant être substitué ;
- iv) le ou les substituant(s) que peut porter les radicaux aryle que représentent Z_{23} et Z_{24} , cycloalkyle et hétéroaryle que représente Z_{24} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , $OCHF_2$, SCF_3 , nitro, cyano, azido, hydroxy, -C(O)O-alkyle, -O-C(O)-alkyle, -NH-C(O)-alkyle, alkylsulfonyle, mono- ou di-alkylamino, amino, aminoalkyle, pyrrolyle, pyrrolydinyne ou bien les radicaux phényle, phénoxy, phénylthio, benzyle, benzyloxy dont le radical aryle est éventuellement substitué par un ou plusieurs radicaux alkyle, CF_3 ou halo ;
- v) le ou les substituant(s) que peuvent porter les radicaux aryle et hétéroaryle que représente Z_{25} sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , OCF_3 , nitro, cyano, -NH-C(O)-alkyle, alkylsulfonyle, amino, mono- et di-alkylamino, phényle, pyridino ;
- vi) le substituant que peut porter le radical alkyle que représente R_3 est le radical cyano.
- vii) le ou les substituant(s) que peut porter le radical aralkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , OCF_3 , $OCHF_2$, SCF_3 , $SCHF_2$, nitro, cyano, -C(O)O-alkyle, alkylsulfonyle, thiadiazolyle, ou bien les radicaux phényle et phénoxy dont le radical phényle est éventuellement substitué par un ou plusieurs radicaux halo.
- viii) le ou les substituant(s) que peut porter le radical hétéroarylalkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo ou nitro.

3. Composés de formule générale I telle que définie à l'une des revendications 1 à 2, caractérisée en ce que

- R_1 représente un radical (C_1-C_6) alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel
- Z_{11} représente un (C_1-C_6) alkyle,

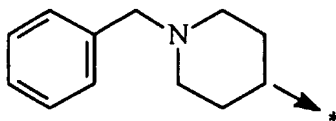
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- 5 Z_{12} représente *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle éventuellement substitué, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, ou bien Z_{12} représente



Y représente l'atome d'oxygène,

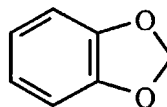
ou bien R_1 représente un radical de formule



- 10 R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical (C_1-C_{15}) alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

- 15 Z_{22} représente cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, pipéridinosulfonyl, $-C(O)-O$ -alkyle, $-C(O)$ -alkyle, ou phényle, ou bien Z_{22} représente un radical de formule



- 20 X_2 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, alkynyle, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_p-U-Z_{24}$ dans lequel

W représente SO_2 ,

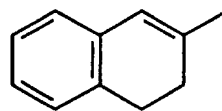
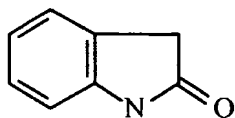
U représente une liaison covalente,

Z_{23} représente un radical aryle ;

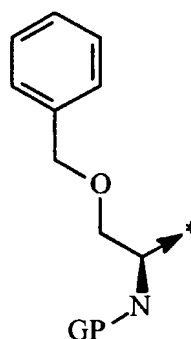
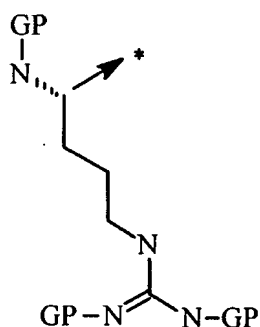
- 25 Z_{24} représente cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle éventuellement substitué par un radical aminoalkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis

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parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{SCF}_3$, hydroxy, $-\text{O}-\text{C}(\text{O})$ -alkyle, mono- ou di-alkylamino, amino ou Z_{24} représente un radical de formule



5 ou bien X_2 représente



X_3 représente un radical $-(\text{CH}_2)_p\text{Z}_{25}$ dans lequel Z_{25} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3 ,

10 R_3 représente l'atome d'hydrogène, un radical alkyle, alkényle, hétéroarylalkyle éventuellement substitué ou un radical de formule $-\text{C}(\text{Y})-\text{NHX}_1$, $-\text{C}(\text{O})\text{X}_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(\text{CH}_2)_p\text{Z}_{22}$ dans lequel

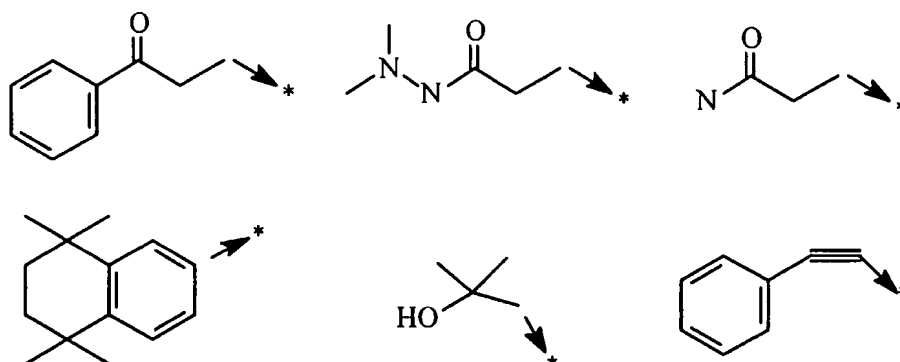
15 Z_{22} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, phénoxy ;

X_2 représente le radical vinyle substitué par un phényle, le radical phényle étant lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(\text{CH}_2)_p\text{-U-Z}_{24}$ dans lequel

20 Z_{24} représente alkyle, $(\text{C}_3\text{-C}_7)$ cycloalkyle, $(\text{C}_3\text{-C}_7)$ hétérocycloalkyle, bis-phényle, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, hydroxy, CF_3 , nitro, amino, mono- et di-alkylamino, pyrrolyle,

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ou bien X_2 représente un radical de formule



X_3 représente un radical (C_1 - C_{10})alkyle linéaire ou ramifié, le radical vinyle substitué par un radical (le radical phényle étant lui-même éventuellement substitué), CF_3 , ou $-(CH_2)_pZ_{25}$ dans lequel

5

Z_{25} représente aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, $-NH-C(O)$ -alkyle, mono- et di-alkylamino.

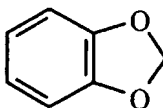
- 10 4. Composés de formule I telle que définie à l'une des revendications 1 à 3, caractérisée en ce que R_1 représente un radical (C_1 - C_6)alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

Z_{11} représente un (C_1 - C_6)alkyle,

15

Z_{12} représente naphthyle, morpholino, *bis*-phényle, pyrrolidinyle substitué par le radical oxy, ou bien les radicaux phényle, pipérazinyle, pyridinyle et indolyle qui sont éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux bromo, fluoro, chloro, alkyle, alkoxy, $-CF_3$, $-OCF_3$;

ou bien Z_{12} représente

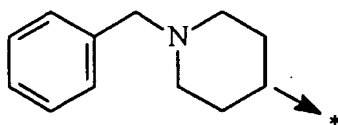


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Y représente l'atome d'oxygène,

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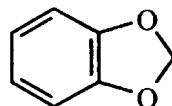
ou bien R_1 représente un radical de formule :



5. Composés de formule I telle que définie à l'une des revendications 1 à 4, caractérisée en ce que R_2 représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

- 10 Z_{22} représente cyclohexyle, cyclohexényle, *bis*-phényle, morpholino, pipéridino, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou phényle, naphthyle ou furyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, pipéridinosulfonyl, $-C(O)-O$ -alkyle, $-C(O)$ -alkyle ou phényle, ou bien Z_{22} représente un radical de formule



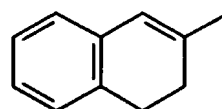
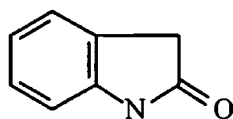
- 15 X_2 représente un radical alkyle, alkynyle, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_pZ_{24}$ dans lequel

W représente SO_2 ;

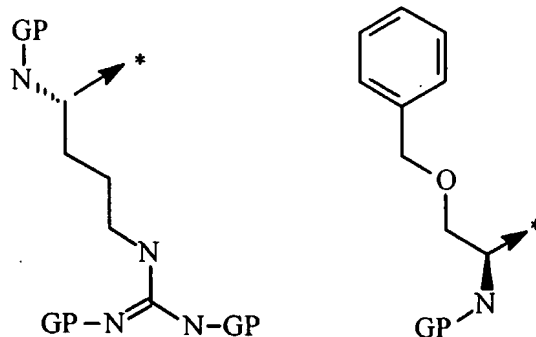
Z_{23} représente le radical phényle ;

- 20 Z_{24} représente cyclohexényle, *bis*-phényle, cyclohexyle éventuellement substitué par un radical aminoalkyle, ou phényle, naphthyle, benzothiényl, thiényl ou indolyle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-CF_3$, $-OCF_3$, SCF_3 , hydroxy, $-O-C(O)$ -alkyle, $-NH-C(O)$ -alkyle, mono- ou di-alkylamino, amino, ou

- 25 Z_{24} représente un radical de formule



ou bien X_2 représente



X_3 représente un radical $-(CH_2)_pZ_{25}$ dans lequel Z_{25} représente le radical phényle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3 .

6. Composés de formule I telle que définie à l'une des revendications 1 à 5, caractérisée en ce que R_3 représente l'atome d'hydrogène, un radical alkyle, alkényle ou furyl-méthyl substitué par un ou plusieurs radicaux nitro, ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical $-(CH_2)_pZ_{22}$ dans lequel

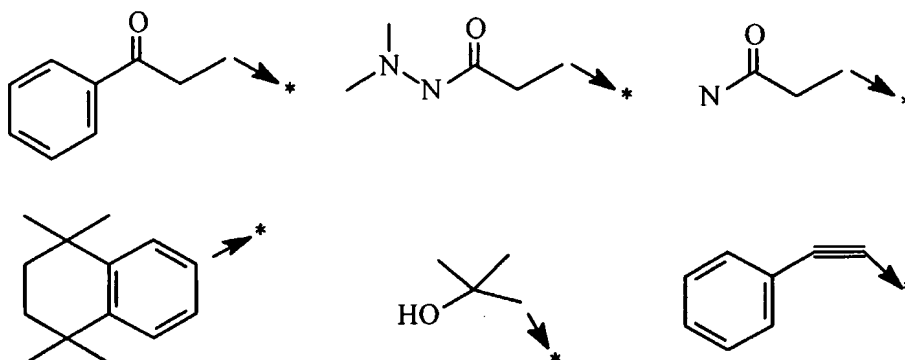
Z_{22} représente le radical phényle ou naphthyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, phénoxy,

X_2 représente le radical vinyle substitué par un radical phényle lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_pU-Z_{24}$ dans lequel

Z_{24} représente alkyle, cyclohexyle, tétrahydrofuryle, bis-phényle, amino, mono ou di-alkylamino, ou phényle, indolyle, thiényl, pyridinyle, benzothiényl et furyl éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, amino, mono- et di-alkylamino, nitro, hydroxy, pyrrolyl

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ou bien X_2 représente un radical de formule



X_3 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, le radical vinyle substitué par un radical phényle, CF_3 , ou $-(CH_2)_pZ_{25}$ dans lequel

- 5 Z_{25} représente un radical phényle, naphthyle, thiényl, pyrazolyle ou thiazolyle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, $-NH-C(O)-$ alkyle, mono- et di-alkylamino.

7. Composés de formule I telle que définie à l'une des revendications 1 à 6, caractérisée en ce que R_1 représente le radical $-(CH_2)_mZ_{12}$ dans lequel $m = 2$ et Z_{12} représente *bis*-phényle ou bien le radical indolyle substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux alkyle et alkoxy.

8. Composés de formule I telle que définie à l'une des revendications 1 à 7, caractérisée en ce que R_2 représente les radicaux de formule $-C(Y)NHX_1$ et $-C(O)X_2$ dans laquelle

Y représente S ;

X_1 représente un radical phényle éventuellement substitué par un ou plusieurs radicaux azido,

X_2 représente $-(CH_2)_pZ_{24}$ dans lequel

- 20 p est égal à 1, 2 ou 3,

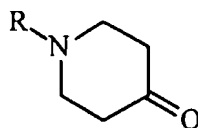
Z_{24} représente cyclohexyle, ou phényle ou benzothiényl éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo ou $-CF_3$.

9. Composés de formule I telle que définie à l'une des revendications 1 à 8, caractérisée en ce que R_3 représente l'atome d'hydrogène ou le radical méthyle.

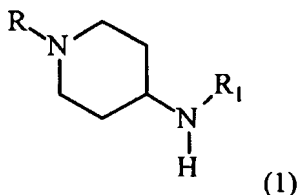
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10. Procédé de préparation, en phase liquide, de composés de formule I telle que définie à la revendication 1, caractérisé en ce qu'il comprend

l'amination réductrice de la pipéridone N-substituée suivante

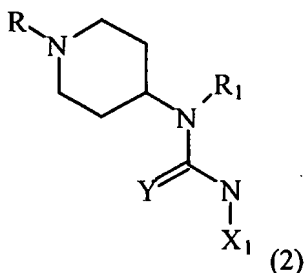


- 5 dans laquelle R représente le radical méthyle ou Boc, en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée à la revendication 1, pour obtenir le composé de formule 1



composé de formule (1) que l'on fait réagir avec

- 10 A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée à la revendication 1, pour obtenir un composé de formule (2)



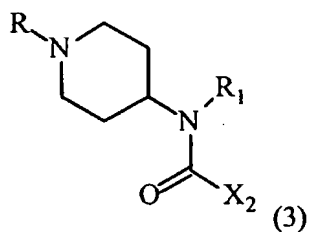
- composé de formule (2) qui représente le composé de formule (I) correspondant dans lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à
- 15 un traitement acide pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1 , Y, X_2 et X_3 ont la signification indiquée à la revendication 1, pour obtenir le composé de formule I

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correspondant dans laquelle R_2 représente un radical de formule $-C(Y)NHX_1$ et R_3 le radical $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 respectivement ;

B) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (3)



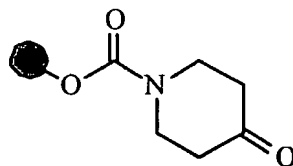
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composé de formule (3) qui représente le composé de formule (I) correspondant dans lequel R_3 représente Me ou Boc et qui, lorsque R_3 représente Boc, peut être soumis à un traitement acide pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

- 10 composé de formule (I) ainsi obtenu que l'on peut faire réagir avec un composé de formule $X_1NC(Y)$, X_2CO_2H ou bien X_3SO_2Cl dans laquelle X_1 , Y , X_2 et X_3 ont la signification indiquée à la revendication 1, pour obtenir le composé de formule I correspondant dans laquelle R_2 représente un radical de formule $-C(O)X_2$ et R_3 le radical $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 respectivement.

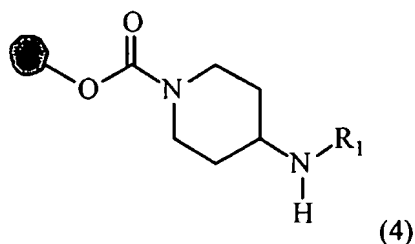
- 15 11. Procédé de préparation, en phase solide, de composés de formule I telle que définie à la revendication 1, caractérisé en ce qu'il comprend

l'amination réductrice de la résine cétonique



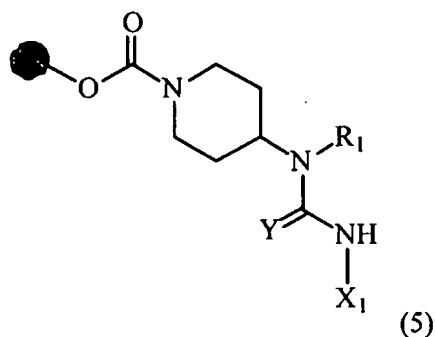
- 20 en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée à la revendication 1, pour obtenir le composé de formule (4)

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composé de formule (4) que l'on fait réagir avec

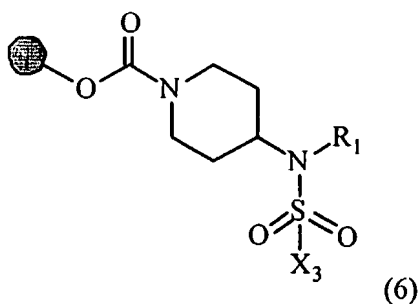
A) soit un composé de formule $X_1NC(Y)$ dans laquelle X_1 et Y ont la signification indiquée à la revendication 1, pour obtenir un composé de formule (5)



5

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (6)

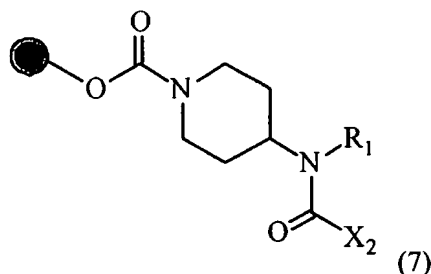


10

suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène,

C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (7)

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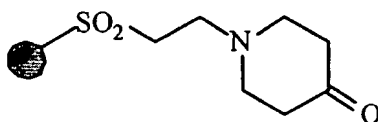


suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène ;

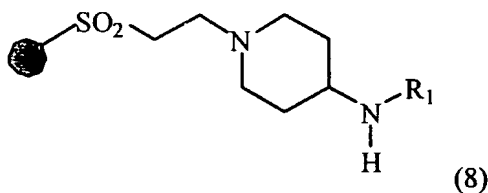
- 5 D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (7) tel que défini ci-dessus, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant dans laquelle R_3 représente l'atome d'hydrogène.

12. Procédé de préparation, en phase solide, de composés de formule I telle que définie à la revendication 1, caractérisé en ce qu'il comprend

- 10 l'amination réductrice de la résine cétonique



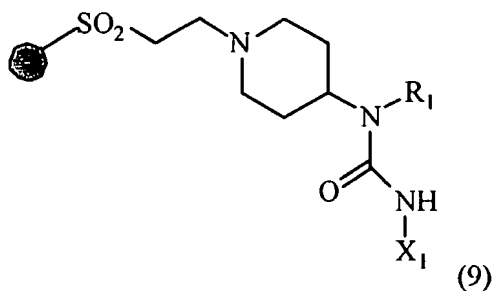
en présence d'une amine de formule R_1NH_2 dans laquelle R_1 a la signification indiquée à la revendication 1, pour obtenir le composé de formule (8)



- 15 composé de formule (8) que l'on fait réagir avec

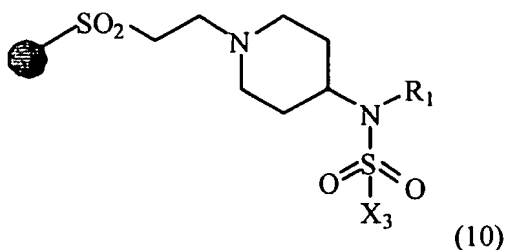
A) soit un composé de formule $X_1NC(O)$ dans laquelle X_1 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (9)

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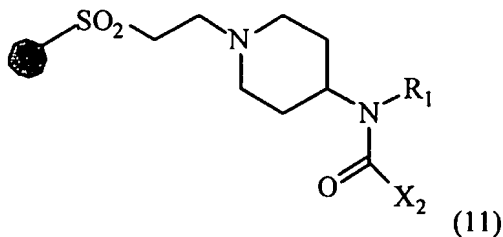
composé (9) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;

- 5 B) soit un composé de formule X_3SO_2Cl dans laquelle X_3 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (10)



- composé (10) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;
- 10

C) soit un composé de formule X_2CO_2Cl dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (11)



- composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant ;
- 15

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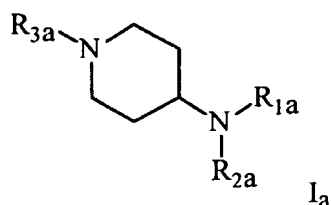
D) soit un composé de formule X_2CO_2H dans laquelle X_2 a la signification indiquée à la revendication 1, pour obtenir un composé de formule (11) tel que défini ci-dessus,

- 5 composé (11) ainsi formé que l'on fait réagir avec un composé de formule R_3X dans laquelle R_3 est tel que défini à la revendication 1 et X représente Br ou I, suivi du clivage de la résine pour obtenir le composé de formule (I) correspondant.

13. A titre de médicaments, les produits de formule I telle que définie à l'une des revendications 1 à 9, ainsi que les sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables desdits produits de formule I.

- 10 14. Compositions pharmaceutiques contenant, à titre de principe actif, un au moins des médicaments tels que définis à la revendication 13, en association avec un support pharmaceutiquement acceptable.

15 15. Utilisation d'un composé de formule générale I_a

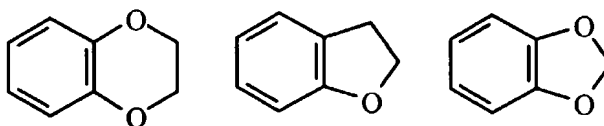


- 15 sous forme racémique, d'énantiomère ou toutes combinaisons de ces formes, dans laquelle :

R_{1a} représente un radical (C_1-C_{16}) alkyle linéaire ou ramifié, alkényle, alkynyle, $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

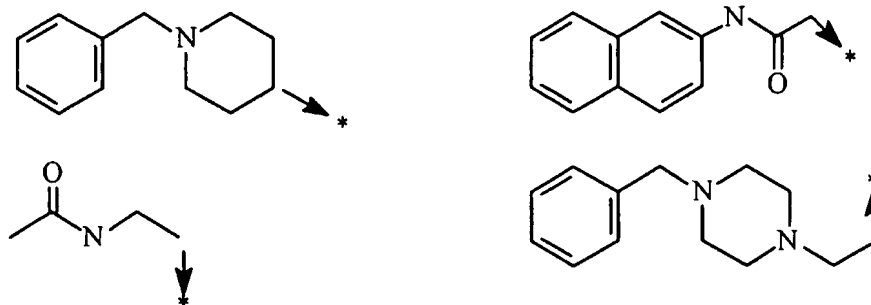
Z_{11} représente un (C_1-C_6) alkyle ou aryle éventuellement substitué,

- 20 Z_{12} représente cyano, cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle éventuellement substitué, aryle éventuellement substitué ou hétéroaryle éventuellement substitué, ou bien Z_{12} représente un radical de formule



ou bien R_{1a} représente un radical de formule

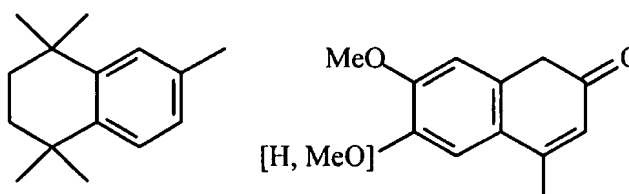
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R_{2a} représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 ;

R_{3a} représente l'atome d'hydrogène, un radical alkyle éventuellement substitué, alkényle, alkynyle, aralkyle éventuellement substitué, hétéroarylalkyle éventuellement substitué, ou un radical de formule -C(Y)-NHX₁, -(CH₂)_n-C(O)X₂,

5 SO_2X_3 ou



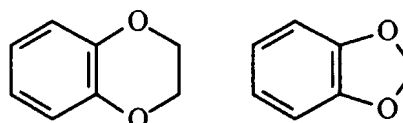
X₁ représente un radical (C₁-C₁₅)alkyle linéaire ou ramifié, alkényle, alkynyle, -(CH₂)_m-Y-Z₂₁ ou -(CH₂)_pZ₂₂ dans lequel

Z₂₁ représente un (C₁-C₆)alkyle

10

Z₂₂ représente cyclohexényle, indanyle, *bis*-phényle, (C₃-C₇)cycloalkyle, (C₃-C₇)hétérocycloalkyle, mono- ou di-alkylamino, -C(O)-O-alkyle, ou aryle ou hétéroaryle éventuellement substitué,

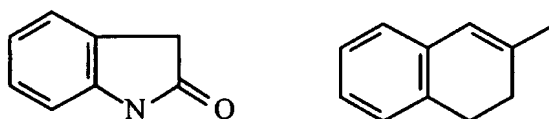
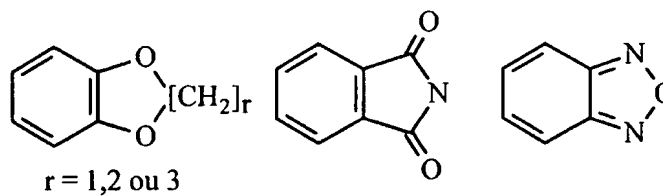
ou Z_{22} représente un radical de formule



15 X₂ représente un radical (C₁-C₁₀)alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), alkynyle, ou un radical de formule -(CH₂)_m-W-(CH₂)_q-Z₂₃ ou -(CH₂)_p-U-Z₂₄ dans lequel

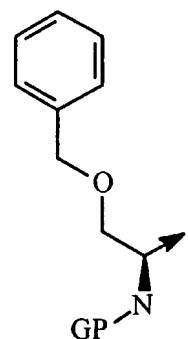
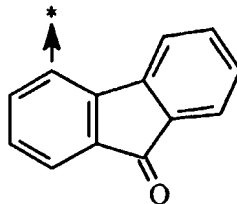
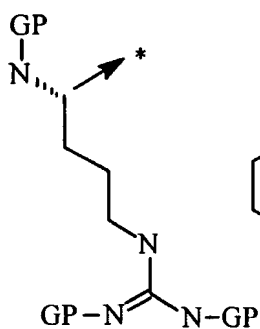
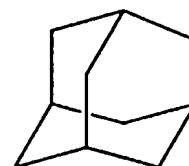
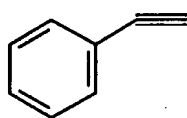
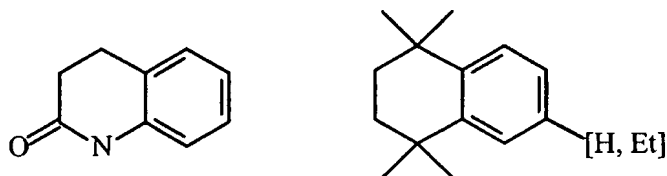
Z₂₃ représente un (C₁-C₆)alkyle ou aryle éventuellement substitué ;

Z_{24} représente alkyle, cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle éventuellement substitué, (C_3-C_7) hétérocycloalkyle, cyano, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué, ou Z_{24} représente un radical de formule

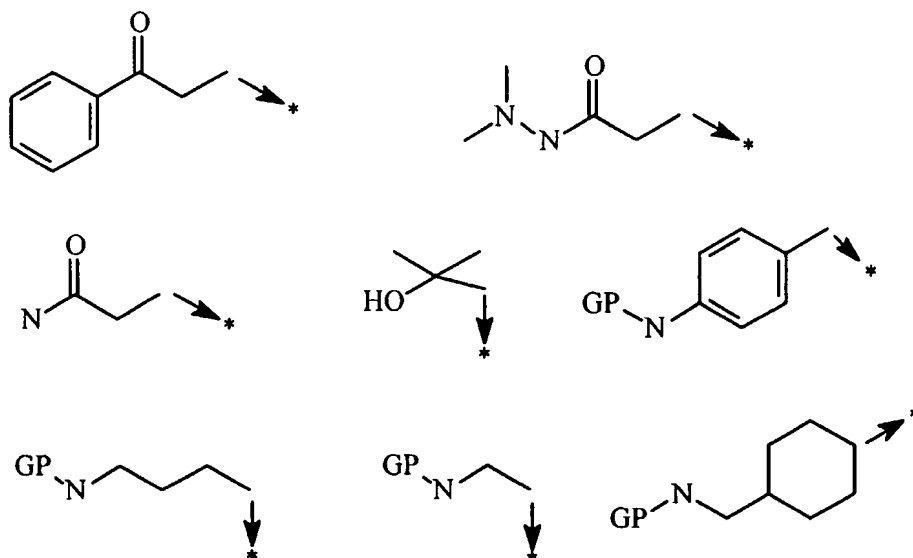


5

ou bien X_2 représente un radical représenté ci-dessous :



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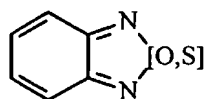


où le groupe protecteur (GP) représente H ou le *tert*-butyloxycarbonyle ;

X₃ représente un radical (C₁-C₁₀)alkyle linéaire ou ramifié, alkényle éventuellement substitué par un radical phényle (le radical phényle étant lui-même éventuellement substitué), CF₃, ou -(CH₂)_pZ₂₅ dans lequel

Z₂₅ représente aryle ou hétéroaryle éventuellement substitué,

ou bien X₃ représente un radical de formule



éventuellement substitué par un ou plusieurs radicaux halo

identiques ou différents ;

Y représente un atome d'oxygène ou de soufre ;

10 W représente un atome d'oxygène, de soufre ou SO₂ ;

U représente une liaison covalente ou l'atome d'oxygène ;

n est un entier de 0 à 4 ;

m est un entier de 1 à 6 ;

p est un entier de 0 à 6 ;

15 q est un entier de 0 à 2,

ou leurs sels d'addition avec les acides minéraux ou organiques pharmaceutiquement acceptables, pour la préparation d'un médicament destiné à traiter les états pathologiques ou les maladies dans lesquels un (ou plusieurs) des récepteurs de la somatostatine est(sont) impliqué(s).

- 5 16. Utilisation des produits de formule générale I_a selon la revendication 15, caractérisée en ce que

i) le ou les substituant(s) que peuvent porter les radicaux aryle que représentent Z₁₁ et Z₁₂ et hétéroaryle que représente Z₁₂ sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, -CF₃, -OCF₃, phényle, phénoxy, aminosulfonyle ;

10 ii) le ou les substituant(s) que peut porter le radical hétérocycloalkyle que représente Z₁₂ sont choisis indépendamment parmi les radicaux oxy et alkyle ;

iii) le ou les substituant(s) que peuvent porter les radicaux aryle et hétéroaryle que représente Z₂₂ sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkényle, alkoxy, alkylthio, CF₃, OCF₃, nitro, cyano, azido, aminosulfonyle, pipéridinosulfonyle, mono- ou di-alkylamino, -C(O)-O-alkyle, -C(O)-alkyle, ou phényle, phénoxy, phénylthio, benzyloxy, le radical phényle pouvant être substitué ;

15 iv) le ou les substituant(s) que peut porter le radical aryle que représentent Z₂₃ et Z₂₄, cycloalkyle et hétéroaryle que représente Z₂₄ sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF₃, OCF₃, OCHF₂, SCF₃, nitro, cyano, azido, hydroxy, -C(O)O-alkyle, -O-C(O)-alkyle, -NH-C(O)-alkyle, alkylsulfonyle, mono- ou di-alkylamino, amino, aminoalkyle, pyrrolyle, pyrrolydinyne ou bien les radicaux phényle, phénoxy, phénylthio, benzyle, benzyloxy dont le radical aryle est éventuellement substitué par un ou plusieurs radicaux alkyle, CF₃ ou halo ;

20 v) le ou les substituant(s) que peuvent porter les radicaux aryle et hétéroaryle que représente Z₂₅ sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF₃, OCF₃, nitro, cyano, -NH-C(O)-alkyle, alkylsulfonyle, amino, mono- et di-alkylamino, phényle, pyridino ;

30 vi) le substituant que peut porter le radical alkyle que représente R₃ est le radical cyano ;

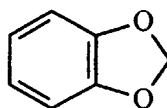
vii) le ou les substituant(s) que peut porter le radical aralkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , OCF_3 , $OCHF_2$, SCF_3 , $SCHF_2$, nitro, cyano, $-C(O)O$ -alkyle, alkylsulfonyl, thiadiazolyle, ou bien les radicaux phényle et phénoxy dont le radical phényle est éventuellement substitué par un ou plusieurs radicaux halo ;

viii) le ou les substituant(s) que peut porter le radical hétéroarylalkyle que représente R_3 sont choisis indépendamment parmi les radicaux fluoro, chloro, bromo ou nitro.

17. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 16, caractérisée en ce que R_{1a} représente un radical (C_1-C_6) alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

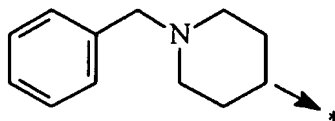
Z_{11} représente un (C_1-C_6) alkyle,

Z_{12} représente *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle éventuellement substitué, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, ou bien Z_{12} représente



Y représente l'atome d'oxygène,

ou bien R_{1a} représente un radical de formule



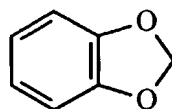
18. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 17, caractérisée en ce que R_{2a} représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X_1 représente un radical (C_1-C_{15}) alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente cyclohexényle, *bis*-phényle, (C_3-C_7) cycloalkyle, (C_3-C_7) hétérocycloalkyle, mono- ou di-alkylamino, $-C(O)-O$ -alkyle, ou

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aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF_3 , OCF_3 , nitro, cyano, azido, pipéridinosulfonyl, $-\text{C}(\text{O})-\text{O}-\text{alkyle}$, $-\text{C}(\text{O})-\text{alkyle}$, ou phényle,
 5 ou bien Z_{22} représente un radical de formule



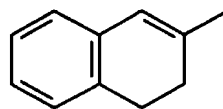
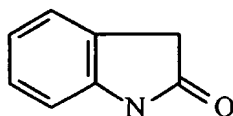
X_2 représente un radical $(\text{C}_1-\text{C}_{10})$ alkyle linéaire ou ramifié, alkynyle, $-(\text{CH}_2)_m-\text{W}-(\text{CH}_2)_q-\text{Z}_{23}$ ou $-(\text{CH}_2)_p-\text{U}-\text{Z}_{24}$ dans lequel

W représente SO_2 ,

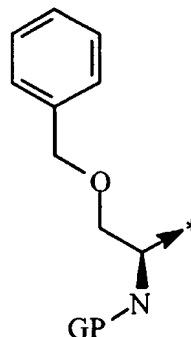
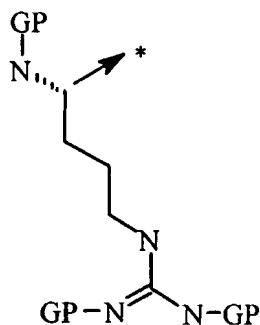
U représente une liaison covalente,

10 Z_{23} représente un radical aryle ;

Z_{24} représente cyclohexényle, bis-phényle, (C_3-C_7) cycloalkyle éventuellement substitué par un radical aminoalkyle, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-\text{CF}_3$, $-\text{OCF}_3$, SCF_3 , hydroxy, $-\text{O}-\text{C}(\text{O})-\text{alkyle}$, mono- ou di-alkylamino, amino
 15 ou Z_{24} représente un radical de formule



ou bien X_2 représente



20 X_3 représente un radical $-(\text{CH}_2)_p-\text{Z}_{25}$ dans lequel Z_{25} représente un radical aryle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3 .

19. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 18, caractérisée en ce que R_{3a} représente l'atome d'hydrogène, un radical alkyle, alkényle, hétéroarylalkyle éventuellement substitué ou un radical de formule -C(Y)-NHX₁, -C(O)X₂ ou SO₂X₃ dans laquelle

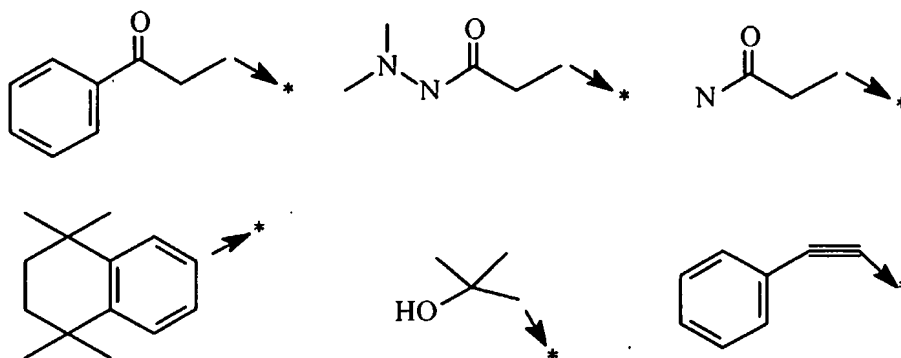
5 X₁ représente un radical -(CH₂)_pZ₂₂ dans lequel

Z₂₂ représente un radical aryle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF₃, nitro, phénoxy ;

10 X₂ représente le radical vinyle substitué par un phényle, le radical phényle étant lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou -(CH₂)_p-U-Z₂₄ dans lequel

15 Z₂₄ représente alkyle, (C₃-C₇)cycloalkyle, (C₃-C₇)hétérocycloalkyle, bis-phényle, amino, mono ou di-alkylamino, ou aryle ou hétéroaryle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, hydroxy, CF₃, nitro, amino, mono- et di-alkylamino, pyrrolyle,

ou bien X₂ représente un radical de formule



20 X₃ représente un radical (C₁-C₁₀)alkyle linéaire ou ramifié, le radical vinyle substitué par un radical (le radical phényle étant lui-même éventuellement substitué), CF₃, ou -(CH₂)_pZ₂₅ dans lequel

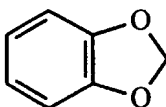
25 Z₂₅ représente aryle ou hétéroaryle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF₃, nitro, -NH-C(O)-alkyle, mono- et di-alkylamino.

20. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 19, caractérisée en ce que R_{1a} représente un radical (C₁-C₆)alkyle linéaire ou ramifié, le radical $-(CH_2)_m-Y-Z_{11}$ ou $-(CH_2)_m-Z_{12}$ dans lequel

Z₁₁ représente un (C₁-C₆)alkyle,

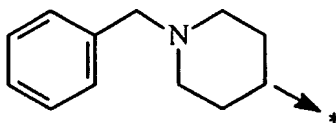
5 Z₁₂ représente naphthyle, morpholino, *bis*-phényle, pyrrolidinyle substitué par le radical oxy, ou bien les radicaux phényle, pipérazinyle, pyridinyle et indolyle qui sont éventuellement substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux bromo, fluoro, chloro, alkyle, alkoxy, -CF₃, -OCF₃ ;

10 ou bien Z₁₂ représente



Y représente l'atome d'oxygène,

ou bien R_{1a} représente un radical de formule ci-dessous :

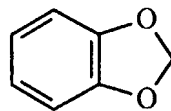


15 21. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 20, caractérisée en ce que R_{2a} représente un radical de formule $-C(Y)NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

X₁ représente un radical (C₁-C₁₀)alkyle linéaire ou ramifié, ou $-(CH_2)_pZ_{22}$ dans lequel

20 Z₂₂ représente cyclohexyle, cyclohexényle, *bis*-phényle, morpholino, pipéridino, mono- ou di-alkylamino, -C(O)-O-alkyle, ou phényle, naphthyle ou furyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, alkylthio, CF₃, OCF₃, nitro, cyano, azido, 25 pipéridinosulfonyl, $-C(O)-O-alkyle$, $-C(O)-alkyle$ ou phényle, ou bien Z₂₂ représente un radical de formule

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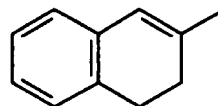
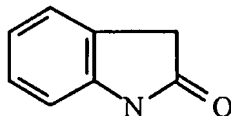
X_2 représente un radical alkyle, alkynyle, $-(CH_2)_m-W-(CH_2)_q-Z_{23}$ ou $-(CH_2)_pZ_{24}$ dans lequel

W représente SO_2 ;

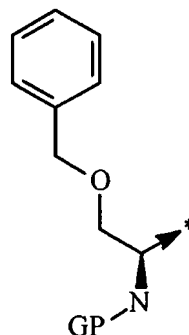
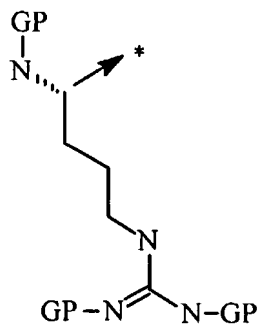
Z_{23} représente le radical phényle ;

5 Z_{24} représente cyclohexényle, bis-phényle, cyclohexyle éventuellement substitué par un radical aminoalkyle, ou phényle, naphthyle, benzothiényne, thiényne ou indolyne éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo, alkyle, alkoxy, $-CF_3$, $-OCF_3$, SCF_3 , hydroxy, $-O-C(O)-$ alkyle, $-NH-C(O)-$ alkyle, 10 mono- ou di-alkylamino, amino, ou

Z_{24} représente un radical de formule



ou bien X_2 représente



15 X_3 représente un radical $-(CH_2)_pZ_{25}$ dans lequel Z_{25} représente le radical phényle éventuellement substitué par un ou plusieurs radicaux identiques ou différents choisis parmi alkoxy et CF_3 .

22. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 21, caractérisée en ce que R_{3a} représente l'atome d'hydrogène, un radical alkyle, 20 alkényle ou furyl-méthyl substitué par un ou plusieurs radicaux nitro, ou un radical de formule $-C(Y)-NHX_1$, $-C(O)X_2$ ou SO_2X_3 dans laquelle

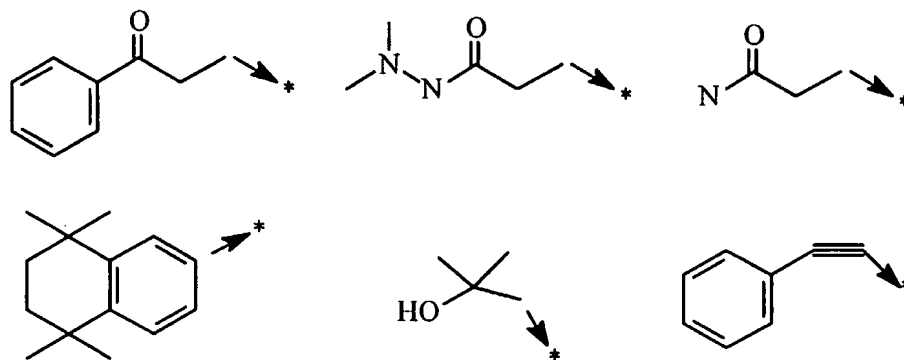
X_1 représente un radical $-(CH_2)_pZ_{22}$ dans lequel

Z_{22} représente le radical phényle ou naphthyle éventuellement substitué par un ou plusieurs radicaux choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, phénoxy,

5 X_2 représente le radical vinyle substitué par un radical phényle lui-même éventuellement substitué par un ou plusieurs radicaux halo, ou $-(CH_2)_p-U-Z_{24}$ dans lequel

Z_{24} représente alkyle, cyclohexyle, tétrahydrofuryle, *bis*-phényle, amino, mono ou di-alkylamino, ou phényle, indolyle, thiényle, pyridinyle, benzothiényne et furyle éventuellement substitué par un ou plusieurs radicaux choisis parmi alkoxy, bromo, chloro, fluoro, amino, mono- et di-alkylamino, nitro, hydroxy, pyrrolyle

ou bien X_2 représente un radical de formule



15 X_3 représente un radical (C_1-C_{10}) alkyle linéaire ou ramifié, le radical vinyle substitué par un radical phényle, CF_3 , ou $-(CH_2)_pZ_{25}$ dans lequel

Z_{25} représente un radical phényle, naphthyle, thiényle, pyrazolyle ou thiazolyle éventuellement substitué par un ou plusieurs substituants choisis indépendamment parmi les radicaux fluoro, chloro, bromo, iodo, alkyle, alkoxy, CF_3 , nitro, $-NH-C(O)-$ alkyle, mono- et di-alkylamino.

23. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 22, caractérisée en ce que R_{1a} représente le radical $-(CH_2)_mZ_{12}$ dans lequel $m = 2$ et Z_{12} représente *bis*-phényle ou bien le radical indolyle substitués par un ou plusieurs substituants choisis indépendamment parmi les radicaux alkyle et alkoxy.

24. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 23, caractérisée en ce que R_{2a} représente les radicaux de formule $-C(Y)NHX_1$ et $-C(O)X_2$ dans laquelle

Y représente S ;

5 X_1 représente un radical phényle éventuellement substitué par un ou plusieurs radicaux azido,

X_2 représente $-(CH_2)_pZ_{24}$ dans lequel

p est égal à 1, 2 ou 3,

10 Z_{24} représente cyclohexyle, ou phényle ou benzothiényne éventuellement substitué par un ou plusieurs radicaux choisis parmi fluoro, chloro, bromo, iodo ou $-CF_3$.

25. Utilisation des produits de formule générale I_a selon l'une des revendications 15 à 24, caractérisée en ce que R_{3a} représente l'atome d'hydrogène ou le radical méthyle.

15 26. Utilisation selon l'une des revendications 15 à 25 pour la préparation d'un médicament destiné à traiter l'acromégalie, des adénomes hypophysaires ou des tumeurs gastroentéropancréatiques endocriniennes dont le syndrome carcinoïde.

INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/FR 00/03497

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/58 C07D409/14 C07D417/14 C07D401/14 C07D405/14
 C07D401/12 A61P5/00 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 22735 A (PASTERNAK ALEXANDER ;PATCHETT ARTHUR A (US); GUO LIANGQUIN (US); Y) 14 May 1999 (1999-05-14) claims 1,5-14; examples ---	1,13-26
A	WO 98 44921 A (PASTERNAK ALEXANDER ;PATCHETT ARTHUR A (US); YANG LIHU (US); BERK) 15 October 1998 (1998-10-15) claims 1,21-35; examples ---	1,13-26
A	DE 27 51 138 A (ANPHAR SA) 24 May 1978 (1978-05-24) page 25 -page 27; claims 1,35 ---	1,13-26
A	DE 25 30 894 A (PFIZER) 5 February 1976 (1976-02-05) examples 10,17,29,33 -----	1,13-26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *&* document member of the same patent family

Date of the actual completion of the international search

25 April 2001

Date of mailing of the international search report

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Bosma, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/FR 00/03497

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RAPPORT DE RECHERCHE INTERNATIONALE

Den Internationale No

PCT/FR 00/03497

A. CLASSEMENT DE L'OBJET DE LA DEMANDE

CIB 7 C07D211/58 C07D409/14 C07D417/14 C07D401/14 C07D405/14
 C07D401/12 A61P5/00 A61K31/445

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)

CIB 7 C07D A61P A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	WO 99 22735 A (PASTERNAK ALEXANDER ; PATCHETT ARTHUR A (US); GUO LIANGQUIN (US); Y) 14 mai 1999 (1999-05-14) revendications 1,5-14; exemples ---	1,13-26
A	WO 98 44921 A (PASTERNAK ALEXANDER ; PATCHETT ARTHUR A (US); YANG LIHU (US); BERK) 15 octobre 1998 (1998-10-15) revendications 1,21-35; exemples ---	1,13-26
A	DE 27 51 138 A (ANPHAR SA) 24 mai 1978 (1978-05-24) page 25 -page 27; revendications 1,35 ---	1,13-26
A	DE 25 30 894 A (PFIZER) 5 février 1976 (1976-02-05) exemples 10,17,29,33 -----	1,13-26



Voir la suite du cadre C pour la fin de la liste des documents



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Y document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

Z document qui fait partie de la même famille de brevets

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25 avril 2001

Date d'expédition du présent rapport de recherche internationale

07/05/2001

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Bosma, P

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs

membres de familles de brevets

Dem internationale No

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